DEPARTMENT OF CLINICAL INVESTIGATION

WILLIAM BEAUMONT ARMY MEDICAL CENTER
EL PASO, TEXAS 79920

FISCAL YEAR 1996 ANNUAL REPORT

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COL IDELLE M. WEISMAN/CPT ANTHONY E. PUSATERI/
MS. ELIZABETH YOUNG

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Department Of Clinical Investigation
William Beaumont Army Medical Center
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13. ABSTRACT *(Maximum 200 words)*

Subject report identifies the research activities conducted at William Beaumont Army Medical Center by investigators who had protocols approved by the Institutional Review Board and the Institutional Animal Care and Use Committee. This report includes all protocols registered within the Department of Clinical Investigation during FY 1995. All known presentations and publications are also included. The research protocols described were conducted under the provisions of AR 40-38 (Clinical Investigation Program); AR 40-7 (Use of Investigational Drugs in Humans and the Use of Schedule I Controlled Substances); AR 70-25 (Use of Volunteers as Subjects for Research); HSC 40-23 (Management of Clinical Investigation Protocols and Reports); and AR 70-18 (The Use of Animals in DoD Programs).

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DEPARTMENT OF CLINICAL INVESTIGATION

Fiscal Year 1996 Annual Report

Department of Clinical Investigation
WBAMC • 5005 N. Piedras St.
El Paso, TX 79920-5001
Phone (915)569-2233 • Fax (915)569-1500

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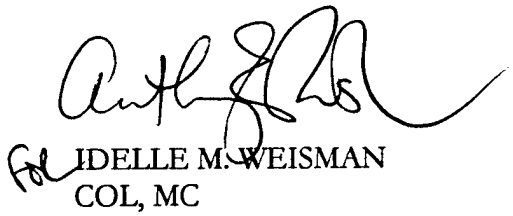
FOREWORD

Fiscal year 96 was another successful year for the Department of Clinical Investigation. Numerous exciting protocols were approved including many for soldier focused research. For example, "Morale Indicators and Dysfunctional Behaviors in Ft. Bliss Soldiers" and "Unexplained Dysnia Related to Bronchial Hyper-reactivity" were two protocols involved with readiness issues of Ft. Bliss soldiers. These protocols were high visibility and received the support of the leadership of Ft. Bliss. These studies respectively evaluated issues directly affecting morale and APFT performance of our number one

FY 96 has been a year of dramatic change, challenge, and success for the Department of Clinical Investigation. By being flexible and adapting to new conditions and expectations, we have continued to succeed. Despite ongoing changes, our department has continued to focus on several key objectives: 1) Provide clinical research mentorship, 2) Provide research laboratory support and expertise, 3) Insure legal, regulatory, and ethical compliance of all WBAMC research, 4) Conduct ongoing medical research in which residents may participate, 5) Support RRC requirements by providing research opportunities through facilitation and conduct of clinical research, 6) Support medical training activities, including medical training involving animals, 7) Establish and promote cooperative research and educational relationships between WBAMC and other medical and educational institutions, 8) Promote an atmosphere of inquiry and critical thinking and an appreciation for the dynamic nature of military medicine, 9) Promote dissemination of scientific findings, 10) Provide scientific means for introducing and evaluating new medical products and processes, 11) Foster development and retention of quality teaching faculty, and 12) Assist investigators in obtaining extramural research funding. As we look to the future, we will continue to focus on the above objectives, with a continued commitment toward self-improvement and dedication to our role in graduate medical education. We look forward to continued success in support of WBAMC in the upcoming year.



IDELLE M. WEISMAN
COL, MC
Chief, Department of Clinical Investigation

DCI

- Immunology/Microbiology Section
- Chemistry Section
- Human Performance Laboratory
- Biological Research Service

Department of Clinical Investigation

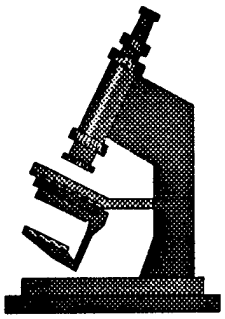
UNIT SUMMARY FY 96

MISSION:

Conduct, coordinate, and augment clinical research and education activities in support of WBAMC mission to provide quality professional clinical services, to conduct graduate medical education programs, and to conduct enlisted AMEDD and Army Nurse training programs. As required, conduct educational, analytical, and clinical research activities in support of other WBAMC and Fort Bliss missions.

TECHNICAL APPROACH:

The Department of Clinical Investigation operates under the guidelines of the Clinical Investigation Program (AR 40-38), Use of Investigational Drugs in Humans and the Use of Schedule I Controlled Substances (AR 40-7), Use of Volunteers as Subjects in Research (AR 70-25), Management of Clinical Investigation Protocols and Reports (HSC Reg 40-23), and The Use of Animals in DoD Programs (AR 70-18). Research protocols utilizing laboratory animals also adhere to the guidelines of the National Academy of Sciences-National Research Council, as described in the "Guide for the Care and Use of Laboratory Animals." Departmental animal research facilities are accredited by the American Association for the Accreditation of Laboratory Animal Care.



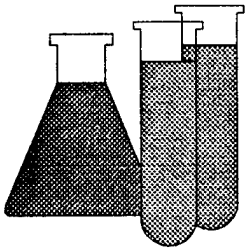
Immunology/Microbiology Section

Research interests of the Immunology and Microbiology Section have been focused on three major areas of research interest - detection and typing of human papilloma viruses in gynecologic tissues, studies of the immunocompetence of splenectomized rats following immunization with pneumococcal polysaccharide vaccine and challenge with *Streptococcus pneumoniae*, and frequency of occurrence of Mycobacteria in paraffin-embedded tissue biopsies from Crohn's disease patients.

Approximately 16,000 American females are diagnosed with

cervical cancer each year. Although routine PAP smears and colposcopy have increased the

determine the frequency of occurrence of Mycobacteria in such cases. PCR amplification of Mycobacterial DNA is used to identify the presence of Mycobacteria and restriction fragment polymorphism mapping of the PCR products then used to identify Mycobacterial species.



Chemistry Section

The chemistry section of DCI is involved in research projects investigating the effect of retinoic acid and liposome-antisense mucin oligomers on mucin gene expression and secretion of mucin in respiratory epithelial cells in culture and repair of epithelial cell injury after exposure to smoke, lipid-mediated fibrinogen and thrombin delivery systems to stop bleeding from tissue injury, status of vitamins in alcoholics, analysis of commercial thrombin preparations and analysis of cross-linked peptides in urine of people suffering from bone disease.

The smoke exposure project is funded by USAMRMC. We have isolated tracheal epithelial cells by incubation with proteases and the cells were successfully cultured in a serum-free and hormone-supplemented medium with retinoic acid. The mucin gene expression and secretion of mucin in these cells were studied in a time-dependent manner. The cells showed normal epithelial features when grown with retinoic acid in the culture medium and mucin gene expresion and secretion remained high. In the absence of retinoic acid, however, the cells did not grow normally and the mucin gene expression was low. The increased mucin gene expression in the cells cultured in medium with retinoic acid as well as mucin hypersecretion was inhibited by a lipid mediated mucin antisense oligomer and the cells were normal. The cells were also exposed to wood smoke for a short period of time. The exposed cells were cultured in the medium with either retinoic acid alone or a combination of retinoic acid and liposome-antisense oligomer in a time-dependent manner. Few cells were seen to detach from the collagen layer in the culture plate immediately after smoke exposure, but the rest of the cells proliferated and differentiated normally when cultured in the complete medium. The results indicated that a combination of retinoic acid and mucin antisense oligomer has the potential clinical application for controlling inflammation, normal cell differentiation and proliferation and inhibition of excessive secretion of mucus in tracheal bronchial cells exposed to toxic substance like smoke.

Recently, in collaboration with MAJ Holcomb of the Department of Surgery and LTC Harris of the Biological Research Service, we have developed a lipid-fibrinogen complex delivery system to stop bleeding from wounds in animals. We are also analyzing both bovine and human commercial thrombin preparations by gel and capillary electrophoresis to check the purity of these materials. These thrombin preparations are used in fibrin dressing sealants to control bleeding from injuries and in some cases the bovine thrombin has been implicated in adverse reactions. We will continue to do work on these interesting projects which has a real potential for clinical application, particularly with wounded soldiers, in the coming year.

We have successfully completed analyzing different vitamins in serum of alcoholics and observed low levels of vitamins, especially A and E, in serum of these patients. After treatment for alcoholism, these vitamins were elevated to normal level. We concluded that vitamins are essential
in maintaining healthy status of people suffering from toxic effects of alcohol consumption.

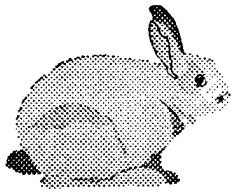
Recently, we have developed a new analytical method for analyzing pyridinoline cross-linked peptides and hydroxylysine-galactose complex found in urine of patients with bone disease. The method involved analysis of these peptides by combination of high pressure liquid chromatography, carbohydrate analyzer and fluorimeter. The development of these new

methodologies will add to our capability of analyzing chemical components in different biological materials.

Human Performance Laboratory

The Human Performance Laboratory at William Beaumont Army Medical Center is a full service cardiopulmonary exercise testing laboratory with

Biological Research Service



The William Beaumont Biological Research Service laboratory animal facility has been fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC) since 1968. Currently, this facility, totaling 7,134 square feet, occupies three buildings on the William Beaumont Army Medical Center (WBAMC) complex. The main facility, in Building 7776, contains the surgical suites, radiology, treatment rooms, necropsy, the majority of the animal holding areas, and the administrative offices. Building 7774, is utilized as a large equipment storage area, plus a 250 square foot, Class 10,000 bioclean room that became operational in FY93 and has been extensively used to maintain rodent colonies with special requirements. The third unit is a 150 square foot, walk-in refrigerator that provides excellent long term storage of rations required by the research animals.

As was true for the past several years, the Biological Research Service has been extremely active in its support of training, research, and collaborative protocols in FY96. Of the presently 39 active protocols, 15 training protocols were supported in FY96 for medical personnel encompassing emergency trauma life support, general surgery, laser surgery, laparoscopic techniques, and vascular microsurgery. Of particular note was the exceptional support provided to the Pediatric Advanced Life Support (PALS) Course, accredited by the American Heart Association. The Advanced Trauma Life Support (ATLS) Course, accredited by the American College of Surgeons, was combined to include trauma personnel from the Texas Tech Medical School and Thomason General Hospital. The combination of these institutions in ATLS training not only serves as a mutual benefit but strengthens the availability and quality of trauma care in the El Paso region.

The 24 research protocols supported by the Biological Research Service were not only practical and militarily relevant, but continued to expand areas of research heretofore lacking at WBAMC. Research continued in the disciplines of microsurgery, soft tissue and orthopedic reconstruction materials and techniques, surgical laser applications, laparoscopic and thoracoscopic methodologies, therapeutic efficacy, molecular biology, and immunology. An area of research with exceptional promise is the collaborative development of a unique dry fibrin sealant dressing (DFSD) for the control of severe hemorrhage. The WBAMC Department of Clinical Investigation and the Biological Research Service continued to take a leading role with the development of a unique non-heparinized liver trauma hemorrhage model for the evaluation of DFSD in grade V liver injuries. Results of this study were excellent. The future phases of the continued development of DFSD will be transferred to the U.S. Army Institute of Surgical Research (ISR) in San Antonio, Texas.

The Biological Research Service, underwent a critical triennial re-accreditation site visit in July 1996 by a team from the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International. Final results of the site visit were received in November 1996 and showed only commendable remarks and no deficiencies. The Biological Research Service has been granted full accreditation until the next site visit in 1999.

Perhaps one of the most exciting and challenging projects in the Biological Research Service is the pending design and construction of a new major addition onto the facility as part of the Life Safety Upgrade Program to the medical center. The design phase is scheduled to be completed in the summer of 1997 and construction to begin in the fall of 1997. The much needed addition will provide the Biological Research Service with greatly increased animal holding areas, a physical plant that meets all AAALAC standards, and expanded surgical and radiological capabilities.

Manpower:

Description	Auth Grade	MOS	Br	Auth	Name	Rank
C, DCI	06	60F	MC	1	Weisman	06
Asst C, DCI	03	71B	MS	1	Pusateri	03
C, Bio Res Svc	04	64C	VC	1	Harris	04
Animal Care NCO	E6	91T		1	Milbradt	E6
Animal Care Sp	E5	91T		1	Charles	E5
Animal Care Sp	E4	91T		1	Stukey	E4
Supv Res Chem	12	1320	GS	1	Bhattacharyya	12
Microbiologist	12	403	GS	1	Veit	12
Chemist	09	1320	GS	1	Enriquez	09
Microbiologist	09	403	GS	1	Smiley	09
Med Technician	07	645	GS	1	Lund	07
Med Technician	07	645	GS	1	Mana	07
Med Technician	07	645	GS	1	McIntyre	07
Health Tech	07	640	GS	1	Revels	07
CI Prot Specialist	09	301	GS	1	Young	07
Sup Clk (Typ)	05	2005	GS	1	Turner	04
Anm Caretaker	04	5048	WG	1	Sigholz	04
Anm Caretaker	01	5048	WG	1	Burton	01

Civilian Personnel with Special Project Funding

Co-Director HP/SCT	Zeballos
Exercise Physiologist	Connery

NOTE: One temporary position that belonged to the Human Performance Laboratory was abolished in Fiscal Year 96.

Department of Clinical Investigation
William Beaumont Army Medical Center

GRANTS FOR FY96

Grant in support "Dry Fibrin Glue Project," MAJ(P) John B. Holcomb and CPT Anthony E. Pusateri. Amount provided from USAMRAA, $25,000.00. Amount provided by Special Project Support Activity, Ft. Belvoir, $7,000.00

Grant in support of Department of Surgery"s surgical training program, LTC Stephen Hetz. Amount provided by Special Project Support Activity, Ft. Belvoir, $5,000.00.

[redacted]

Department of Clinical Investigation
William Beaumont Army Medical Center

Payments Through Non-Federal Sources received in FY96.

Traveller	Department	Dates of TDY	Destination	Provider	Payment	Amount

EXPENDITURES:

	FY94	FY95	FY96
Personnel (Civ)	510,723	481,827	488,018
Consumable Supplies	152,517	130,977	113,848
Capital Equipment	9,313	17,125	4,844
TDY	3,966	6,660	3,285
Printing & Publications	1,066	-0-	-0-
MEDCASE Equipment	64,532	27,296	102,584
Military Pay	491,485	491,485	491,485
TOTAL	1,239,602	1,155,370	1,204,064

PROTOCOLS:

Protocol FY	Ongoing	New	Completed	Terminated	Inactive
FY 94	91	44	28	31	
FY 95	75	60	26	42	
FY 96	60	24	16	30	3

DEPT OF CLINICAL INVESTIGATION

Publications:

Weisman IM, Zeballos RJ. Cardiopulmonary Exercise Testing. Pulmonary/Respiratory Therapy Secrets, Parson and Heffner, Editors. Hanley and Belfus (Mosby), publishers. In Press, 1996

Weisman IM, Zeballos RJ. Clinical Evaluation of Unexplained Dyspnea. Cardiologia 1996; 41:621 634.

Presentations:

Enriquez JI, Bhattacharyya SN, Restrepo A, Knight C.: The analysis of Plasma Vitamin E and Vitamin A by Use of High Precision Liquid Chromatography in Patients Before and After A Alcohol Rehabilitation Program, Presented at the 48th Annual Meeting of the American Association for Clinical Chemistry, August 1, 1996.

Ramirez OE, Bhattacharyya S, Manna B, Rubin BK. Sputum Fucose and Sialic Acid Levels Correlate with Pulmonary Functions and Sputum Biophysical Properties. Presented at the American Thoracic Society, May 11-15, 1996.

Abstract:

Sputum Fucose and Sialic Acid Levels Correlate with Pulmonary Functions and Sputum Biophysical Properties. OE Ramirez, S Bhattacharyya, B Manna, BK Rubin. Am J of Resp Critical Care Medicine, 15b Vol 4, April 1996.

Connery SM, Zeballos RJ, Pusateri, AE, Taylor MB, Weisman, IM. VO2/ WR during Cycle and Arm Crank Ergometry. FASEB Journal 1996; 10:A377.

Pusateri, AE, Marchitelli, LJ, Whitehead, HR, Cline, AD. Incidence of menstrual abnormalities in female soldiers. FASEB Journal 1996; 10:A337.

Marchitelli, LJ, Pusateri, AE, Westphal, KA, Whitehead, HR. Iron status of four populations of U.S. Army women. FASEB Journal; 10:A250

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

Publications:

Carlson JW, Saltzman A, Carter J, Hartenbach E, Johnson P, Chen, MD, Carson LF, Twiggs LB. Squamous Cell Carcinoma Arising in a Neovagina Constructed from a Rectus Abdominis Myocutaneous Flap. *Gynecol Oncol* 1995; 59:159-161.

Hartenbach EM, Saltzman AK, Carter J, Fowler JM Carlson JW, Hunter DW, Twiggs LB, Carson LF. Nonsurgical management strategies for the functional complications of ileocolonic continent urinary reservoirs. *Gynecol Oncol* 1995 59(3): 358-63.

Carlson JW, McGlennen RC, Gomez R. Longbella C, Carter JR, Carson LF. Sebaceous Carinoma of the Vulva: A case report and review of the literature. *Gynecol Oncol* 1996; 60: 489-491.

Maxwell GL, Soisson AP, Harris RA, Miles P. Brittain PC, Carlson J: Repair of transversely incised anterior abdominal rectus fascia: Optimization of technique using a rabbit model. *Obstet Gynecol* 1996; 87:65-68.

Carlson JW, Carter JR, Saltzman AK, Carson LF, Fowler JM, Twiggs LB. Gynecologic Reconstruction with a Rectus Abdominis Myocutaneous Flap: An Update. *Gynecol Oncol* 1996; 61:364-368.

Presentations:

Gynecologic Oncology CREOG Review, Part I, Resident Lecture Series. William Beaumont Army Medical Center. El Paso TX, December 21, 1995.

Gynecologic Oncology CREOG Review, Part II, Resident Lecture Series. William Beaumont Army Medical Center. El Paso TX, December 26, 1995.

Management of the Adnexal Mass, EHSSA Military Medical Surgical Congress, Willingen, Germany April 15,

Laparoscopic Staging of Gynecologic Malignancies, EHSSA Military Medical Surgical Congress, Willingen, Germany April 15, 1996

1996 Gynecologic Monitoring of Patients on. Tamoxifen, EHSSA Military Medical Surgical Congress, Willingen, Germany April 16, 1996

Should You LEEP Before You Look, EHSSA Military Medical Surgical Congress, Willingen, Germany April 17, 1996

Pelvic Masses, September 1996, WBAMC Department Presentation.

Laparoscopic Burch Retropubic Urethropexy Training In A Porcine Model. Allen Walker, CPT, MC, USA. Resident; Julius Szigeti, MAJ, MC, Staff. 35th ACOG Meeting of Armed Forces District, October, 1996, Nashville, TN.

The Absence Of Human Papilloma Virus In Amniotic Fluid. Maxwell GL, CPT, USA; Zalcarean M, Resident Soisson AP; Harlass F; Veit B; Hoshaw N, CPT, USA, Resident; Carlson JW, MAJ. 35th ACOG Meeting of Armed Forces District, October, 1996, Nashville, TN.

Idiopathic Elevated Testosterone Associated With Clitoromegaly: A Case Report And Review Of The Literature. Allen Walker, CPT, MC, USA, Resident; Barbara Jennings, MAJ, MC, USA, Resident; Ruben

Hematosalpinx With Pelvic Pain Following Endometrial Ablation: A Case Report And Confirmation Of The Post-Ablation Tubal Sterilization Syndrome. Joel C. Webb, CPT, MC, USA; Mark R. Bush, CPT, MC, USA; Michael D. Wood, MAJ, MC, USA; Gordon S. Park, COL, MC. 35th ACOG Meeting of Armed Forces District, October, 1996, Nashville, TN.

Unilateral Labial Edema In Early Pregnancy: A Case Report. Kristine A. Eule-Swider, Cpt, MC, USA, Resident; Jay Carlson, Maj, MC, USA, Staff. 35th ACOG Meeting of Armed Forces District, October, 1996, Nashville, TN.

An Initial Experience With Paraurethral Fascial Sling Urethropexy For Genuine Stress Urinary Incontinence. Kristine A. Eule-Swider, Cpt, MC, USA, Resident; Julius Szigeti II, Maj, MC. 35th ACOG Meeting of Armed Forces District, October, 1996, Nashville, TN.

Cervical Chlamydial Screening During Pregnancy In A Military Population. Michael J. Schifano, CPT, MC, USA, Resident; Katherine Foley, MAJ, MC. 35th ACOG Meeting of Armed Forces District, October, 1996, Nashville, TN.

Characterization of Uptake of Technetium-99m Methylene Diphosphonate By Pelvic Soft Tissues During Three Phase Bone Scintigraphy: Preliminary Data
N Hoshaw, Cpt, MC, USA, Resident; J Behan, Cpt, MC, USA, Resident; J Carlson, Maj, MC. 35th ACOG Meeting of Armed Forces District, October, 1996, Nashville, TN.

The Role of Three Phase Bone Scintigraphy in the Evaluation of Women with Chronic Lower Back, Pelvic or Hip Pain of Unknown Etiology: Preliminary Data. Natalie J. Hoshaw, Cpt, MC, USA, Resident; Joseph P. Behan, Cpt, MC, USA, Resident; Carlos E. Jimenez, Cpt, MC, USA, Fellow; Elmer J. Pacheco, LTC, MC, USA, Staff; Albert J. Moreno, COL, MC, USA, Staff; Jay W. Carlson, Maj. 35th ACOG Meeting of Armed Forces District, October, 1996, Nashville, TN.

The Role of the Inflammatory and Dysplastic Pap Smear in Preterm Delivery. Nathan Tillotson, Cpt, MC, USA, Resident; J. Scott Bembry, Cpt, MC, USA, Staff; Seth Borquaye, Cpt, MC, USA, Resident; Michael Schifano, Cpt, MC, USA, Resident; Connie Butterfield, Maj, MC, USA, Staff; Jay Carlson, Maj. 35th ACOG Meeting of Armed Forces District, October, 1996, Nashville, TN.

Laparoscopic Burch Retropubic Urethropexy: Initial Results. Pamela A. Schmagel, CPT, MC, USA, Resident; Joseph P. Behan, CPT, MC, USA, Resident, Julius Szigeti II, MAJ, MC. 35th ACOG Meeting of Armed Forces District, October, 1996, Nashville, TN.

A Comparison Of Laparoscopic Knot Strength. Robert T. Zabenko,CPT, MC, USA, Resident; Jay Carlson, MAJ, MC, USA, Staff; Julius Szigeti II, MAJ, MC, USA, Staff; Anthony Pusateri, CPT, MSC. 35th ACOG Meeting of Armed Forces District, October, 1996, Nashville, TN.

A Minimal Stimulation Induction Protocol: Initial Presentation Of Results And Cost-Efficacy. Scott A. Joyner, CPT, MC, USA, Resident; Ruben Alvero, MAJ, MC. 35th ACOG Meeting of Armed Forces District, October, 1996, Nashville, TN.

Recurrence Of Initially Microscopic Carcinosarcoma: A Report Of Two Cases. Scott A. Joyner, CPT, MC, USA, Resident; Harvey Greenberg, Staff, Jay W. Carlson, Maj, MC. 35th ACOG Meeting of Armed Forces District, October, 1996, Nashville, TN.

Maxwell GL, Carlson JW. Intrapartum Management in Managing Osteogenesis Imperfecta: A Medical Publication for Affected Persons. *(In Press)*

Maxwell GL, Soisson AP, Harris RA, Miles P. Brittain PC, Carlson J: Repair of transversely incised anterior abdominal rectus fascia: Optimization of technique using a rabbit model. *Obstet Gynecol* 1996; 87:65-68.

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Publications:

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DEPARTMENT OF SURGERY

GENERAL SURGERY SERVICE

Publications:

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Craig, R, Kontny, D, O'Donnell: Endovascular Stenting for Iliac Artery Stenosis. Presented at 89th Annual Scientific Assembly of the Southern Medical Assocation, November 1995.

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PROTOCOLS

FOR

FISCAL YEAR

DEPARTMENT OF CLINICAL INVESTIGATION

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): Sam Bhattacharyya, PhD

PROTOCOL TITLE: Human Tracheal Mucin: Biochemical, Physical and Rheological Studies

PROTOCOL #86/17 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): B Manna, JI Enriquez

Key Words: Tracheal Mucin, Human

Study Objective: This protocol is concerned with isolation, purification and characterization of mucin glycoprotein components (mucins) from tracheal secretion of patients with asthma, chronic bronchitis and cystic fibrosis. The glycosylated and nonglycosylated peptides will be isolated, purified and sequenced (peptide portion) after subjecting the purified mucins with different proteolytic enzymes. Antibodies will be developed in rabbits against the nonglycosylated peptides which, in turn, will be used to follow the synthesis and secretion of these macromolecules in a tracheal (or bronchial) culture system. Finally, the viscoelastic properties of purified mucins will be investigated.

Technical Approach:

1. Collect sputum from patients (either male or female, any age) with asthma, chronic bronchitis and cystic fibrosis.
2. Solubilize mucins with water and buffer.
3. Establish the homogeneity of mucin glycoproteins isolated from sputum of patients with asthma, chronic bronchitis, and cystic fibrosis by molecular sieve and ion-exchange chromatography.
4. Isolation and characterization of peptides (or glycopeptides) derived from digestion of mucins with different proteolytic enzymes (Column and HPLC);
5. Amino acid sequence analysis of these peptides by sequenator and DNA cloning procedure;
6. Raise antibodies in rabbits against these peptides (preferably against nonglycosylated peptides); and finally,
7. Establish a tracheal (or bronchial) culture system to examine the synthesis and control in secretion of these macromolecules by ELISA or radioimmunoassay (RIA) procedures using these antibodies.

In addition to the above, the physical properties of mucins, particularly their interaction (in terms of viscosity) with other serum proteins (such as albumin, immunoglobulin, and fibronectin) will be studied.

laboratory in collaboration with Duke University (Durham, NC) and University of Nebraska Medical Center (Omaha, NE) investigators, are now sequencing the complete mucin gene. Estimated completion date has changed from Oct 96 to Oct 97.

DEPARTMENT OF CLINICAL INVESTIGATION

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): Sam Bhattacharyya, PhD

PROTOCOL TITLE: Cellular Mechanism of Mucin Secretion: Studies Involving Rat and Rabbit Tracheal Culture System

PROTOCOL #89/16A STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): B Manna, JI Enriquez

Key Words: Mucin, Animal

Study Objective: This proposal is concerned with the isolation and characterization of mucin glycoprotein components (mucin) from secretions of rat and rabbit tracheal epithelial cells in culture and establishing their structural identity.

Technical Approach: Growth of epithelial cells from rat and rabbit bronchial tissues: Rats and rabbits will be euthanized and normal appearing tracheal tissues excised aseptically, immersed in cold, sterile L-15 culture medium containing penicillin\streptomycin and transported on ice to the laboratory. Lung tissue is sterilely trimmed away and the bronchus cut into large fragments. Cells are isolated from the human bronchus after an overnight incubation with 0.1% protease solution in minimal essential medium (MEM, Ca++free) done at 4 degrees C. The next day, incubated bronchi are flushed with MEM plus 10% Fetal Calf Serum to remove the digested cells. The cells are washed several times to remove any protease, which is toxic to epithelial cultures. The cell suspension is filtered through a sterile 100U nitrex filter and centrifuged for 10 minutes. Cell pellets are resuspended in cold MEM with 10% FCS and centrifuged again. The cold protease overnight treatment is sufficient to remove most epithelial cells lining the bronchus without much contamination of other cell types from the layer under the basement membrane. After the total cell count is taken, primary cultures are normally initiated by plating 1-2x 10 6 cells per ml per 35mm culture dish. The culture conditions used for the human bronchial epithelial cells consist of M199 media with D-valine substituted for D1-valine, 10% Fetal Calf Serum, L-glutamine, penicillin/streptomycin, gentamicin, insulin, transferrin, epidermal growth factor, hydrocortisone, cholera toxin, bovine hypothalamus extract, and fungizone. Primary epithelial cultures were then placed in an incubator, with conditions of 37 degrees C., 5% C, and 95% air, and cells allowed to adhere to the culture dish. After 3-4 days incubation, a confluent primary culture of epithelial cells is routinely observed. The cultures received media change and can be used in various studies.

Construction and screening of the DNA library utilizing human antiapomucin will be done as described.

Control in secretion of mucin: The synthesis of mucin in epithelial culture will be followed by ^{3}H glucosamine and ^{35} SO4 incorporation. The control in synthesis will be studies on transcriptional and translational levels using different inhibitory (acetylcysteine and cyclohexamide) and enhancing (pilocarpine) reagents.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).
Amendment (Jan 94): Time extended to Oct 94. Additional number of rabbits is required to complete project.

Progress: Changes in ultrastructural characteristics and mucin gene expression were examined in rat tracheal explants cultured in a synthetic medium± retinoic acid (RA), benzo [a]pyrene (B[a]P) and N-methyl-N-nitrosourea (NMNU). In the RA(+) cultures, no changes in either ultrastructural features or mucin gene expression were detected after 48h incubation. After 96h incubation, however, the ultrastructural features associated with the squamous phenotype were characteristics of cultures containing two carcinogens and the mucin gene expression was slightly reduced. Thus, in the presence of retinoic acid, the carcinogen induced changes in cytology to the squamous phenotypes were not matched by a marked loss of mucin gene expression. Explants cultured for 48h without RA and ± carcinogens showed none of the cytological changes associated with onset of the squamous phenotype. While mucin mRNA was still detected, it was clearly reduced compared to 48h cultures in RA(+) medium. However, 48h later, all explants exhibited pronounced squamous metaplasia and the mucin message decreased to trace levels. Thus, the results of these experiments with B[a]P and NMNU in RA(+) and RA(-) media indicated that at least the early carcinogen induced changes may be distinct from those associated with the retinoid pathway controlling expression of the mucin component of the mucociliary epithelium. The estimated completion date has changed from Oct 96 to Sep 97. This work has been accepted for publication in the Journal *Inflammation* in 1996.
Publication: Manna B, Ashbaugh P, Kaufman B, and Bhattacharyya SN: Effect on Retinoic Acid on Mucin Gene Expression in Rat Airways in Vitro. Biochemical Journal (London) 1994, 297:309-313.
SN Bhattacharyya, B Manna, P Ashbaugh, and B Kaufman: Effect of Carcinogenic Agents in Retinoic Acid Regulated Mucin Gene Expression in Rate Tracheal Explants in Culture. Inflammation,1995.
Reference:
Bhattacharyya SN, Ashbaugh P, Lund M, Manna B: In vitro effects of drugs on production of mucin in rabbit tracheal epithelial cells expressing mucin gene. Inflammation 16:371-382, 1992.

DEPARTMENT OF CLINICAL INVESTIGATION

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): Sam Bhattacharyya, PhD

PROTOCOL TITLE: Acute Airway Injury and Response: Combined Effect of Smoke and Combustion Products on Mucin Gene Expression and Regulated Mucin Production in the Tracheal-Bronchial Epithelium

PROTOCOL #94/08A STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): MA Nadjem, P Ashbaugh, F Rodriguez, R Coutinho, M Herawi

Key Words: Airway Injury, Smoke

Study Objective: For several years, we at DCI, WBAMC, have studied the characteristics and synthesis of respiratory mucins. One goal, which has now been accomplished, was to study the structure of the protein portion of these macromolecule and raise an antibody against mucin protein core (22). The other goal, now in progress, is to study the regulation of mucin synthesis as well as control of differentiation and proliferation of tracheal epithelial cells in culture (both organ and isolated cell) and ability of different reagents, such as retinoids, different respiratory drugs and mucin antisense oligodeoxynucleotide to intervene effectively with this process and thereby aid patients with chronic as well as acute respiratory problems due to exposure to different noxious substances. To date, we have found that retinoids are required for normal function of tracheal epithelial cells when grown in a serum-free and hormone-supplemented medium. Without retinoic acid, the cells neither expressed mucin message nor maintained normal cytological appearance. When retinoids were added back to the culture medium, the cells grew normally and the mucin message was expressed again (13). Effects of adding pharmacologic agents, such as atropine, histamine, methacholine, phenylephrine, cimetidine, prednisolone and more recently mucin antisense oligodeoxynucleotide to the culture on the growth, differentiation and mucin mRNA level are currently under study -- the most interesting result to date being a marked reduction in mucin mRNA level by prednisolone. In sum, our laboratory, with aid of consultant Dr. Bernard Kaufman of Duke University Medicall Center, Durham, North Carolina, is studying the control of production of respiratory mucins on the cellular as well as molecular level and our specific aims of this project are as follows:

1) Study mucin mRNA expression and mucin secretion in rabbit tracheal cultures exposed to smoke (total smoke, filtered smoke and particulate) generated by burning wood and cotton, singly or in combination, in our inhalation chamber in a time and dose dependent manner. Before exposure, the cell culture will be maintained in a serum-free and hormone-supplemented medium with or without retinoids.

2) Examine the extent of injury to the cells by histologic and ultramicroscopic methodology, i.e., whether converted to squamous or more mucus producing cells.

3) Investigate the effect of addition of retinoids to the retinoid-deficient medium on the nature of the cells as well as the mucin message. The reason for studying separately the effect of filtered gases and particulate is to differentiate between two sources so that we can ascertain the extent of injury contributed by each of them and extent of cure process enhanced by retinoids.

4) Study the effect of pharmacologic agents, such as atropine, cromolyn sodium, steroids and mucin antisense oligodeoxynucleotide on the mucin mRNA level as well as on cell differentiation and proliferation of the tracheal culture exposed to smoke as stated above.

5) Study the effect of retinoids and other agents, as described above, on the injury and mucin synthesis and secretion in trachea of whole rabbits exposed to smoke in our nose-only exposure chamber.

6) Produce an immortal mucin-producing cell line by transfecting the primary tracheal epithelial cells with different nonpathogenic viruses.

7) Examine the effect of long-term exposure of smoke on these cells in terms of their differentiation and expression of mucin message and the effect of retinoids and other agents on this process. Primary tracheal epithelial cells in culture stop producing mucins or sometimes do not survive when maintained in culture medium for more than three to four weeks. The immortalized cell lines will provide us with a system to study long-term effect of smoke-related exposure on mucus production and cell injury at the same time.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Isolated rabbit tracheal epithelial cells have been successfully cultured in a synthetic medium with and without retinoic acid. The culture at 140h was exposed to smoke from pine wood for 2 ½ minutes and contained culture for several days more in the medium with retinoic acid. Examination of the culture indicated loss of cells but the cells regenerated quickly. Morphological examination indicated flattening of cells throughout the culture. Addition of mucin antiSence DNA to the culture maintained columnar nature of the cells. Mucin gene expression has normal throughout the incubation of the epithelial cell in culture. We observed that the effect of anti-sense oligomer was transient in nature. We have now developed a liposome-DNA complex to deliver DNA into the culture more efficiently. Experiments are in progress. The first part of the project, namely exposure of wood smoke to rabbit explants, has been completed and will shortly be communicated to the Journal. Estimated completion date has changed from Sep 96 to Oct 97.

Publication: Manna B, Ashbaugh P, Bhattacharyya: Retinoic Acid-Regulated Cellular Differentiation and Mucin Gene Expression in Isolated Rabbit Tracheal Epithelium Cells in Culture. Inflammation 1995. 19:489-502.

DEPARTMENT OF CLINICAL INVESTIGATION

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): Sam Bhattacharyya, PhD

PROTOCOL TITLE: Relationship of Alcohol-altered Cytokine Levels and Vitamins in Serum of Patients and Patterns of Induction of Alcohol-Mediated Disease

PROTOCOL #95/21 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): JI Enriquez, BC Veit, SK McIntyre, GE Philbin, A Restrepo

Key Words: Vitamin, Alcoholics

Study Objective: The objective of this study is to analyze TNF and vitamins A, C, E and B_6, in the plasma of patients with alcohol abuse and establish a meaningful relationship between the cytokine and antioxidant levels affected by alcohol consumption. Accurate analyses of these components and statistical interpretation of data may result in new approach in systematic treatment of these patients.

Technical Approach: The subjects selected for this study will be from groups of patients admitted to the hospital for treatment of alcohol-related problems. Numerical numbers will be assigned to the patients so that their names will not be known to others except to the doctors treating these patients. Only age, duration of alcohol consumption and severity of diseases will be known to those who will analyze the components in plasma.

Blood will be collected by venipuncture at the time of admission to the study and 30 days later. Serum components for clinical evaluation will be analyzed in the clinical laboratory of the hospital. Plasma samples for the determination of cytokine and antioxidants will be collected by venipuncture using Vacutainers or syringe containing Li-heparin or Na_2EDTA, immediately protected from exposure to light and then, without delay, taken to the laboratory at DCI where the formed elements will be removed by centrifugation and the plasma will be aliquoted in small volumes and frozen in dark tubes at -70^{o}C until the time of assay.

Plasma TNF will be measured by kit ELISA (T-Cell Science, Cambridge, MA), as described (6). The assay has a detection limit of 10 pg/ml. High precisions liquid chromatography (HPLC), employing both spectrophotometric and amperometric detection methods, will be utilized for the analysis of the antioxidants and pyridoxal 5'-phosphate (PLP), the active cofactor of vitamin B6. Detection limits for the HPLC methods are well below normal physiological ranges for the antioxidants and PLP.

Progress: Analyses of Vitamins E and A were done accurately by HPLC procedure in Serum of blood from alcoholics before and after treatment. It was concluded that in the beginning of the treatment phase, the interaction between Vitamins E and A was greater because of the weakened nutritional status common in alcoholic patients. This relationship was less intense after a treatment program, which included abstinence from alcohol and proper nutrition, because a more stable equilibrium between these vitamins was attained. Level of TNF and with other unstable vitamins could not be measured accurately because these compounds degraded quickly during the isolation of serum. These results were presented in August 1996 at the Annual meeting of the American Association for Clinical Chemistry, Chicago, IL. This project was terminated Oct 96.

DEPARTMENT OF CLINICAL INVESTIGATION

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): LTC Richard A. Harris

PROTOCOL TITLE: Combat Trauma Life Support Procedure in the Sheep Model

PROTOCOL #88/52A STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): A Montes

Key Words: Life support, Combat trauma

Study Objective: To train Physicians Assistants and Line Medics who are not dealing with major trauma on a day-to-day basis, but may be called upon to perform this function in a combat environment. The sheep model will simulate human trauma.

Technical Approach: Animal procedures include:

1. Cricothyroidotomy
2. Venous Cutdown
3. Intubation
4. Chest Trauma Management
    a. Needle decompression
    b. Tube thoracostomy

ATLS training manuals will be used for each training procedure.

Progress: A total of 12 combat medics and physician's assistants completed the ATLS program under this protocol FY94. After action reports and critiques indicated that this training was very well received and judged as extremely valuable in familiarizing emergency medical personnel in actual hand-on life saving techniques.

DEPARTMENT OF CLINICAL INVESTIGATION

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): LTC Richard A. Harris

PROTOCOL TITLE: Emergency Life Support Training for Combat Medics in the Small Ruminant (Ovine or Caprine) Animal Model

PROTOCOL #92/11A STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): J Walls

Key Words: Emergency Life Support

Study Objective: This training will enhance the combat Medical aidman's (Medic's) capabilities of administering emergency lifesaving procedures to patients with emergency Medical conditions which require establishment of airways, venous access, and chest trauma management.

Technical Approach: The emergency life support training program is designed for medics who are responsible for providing first to third echelon care to the critically injured patient (echelon 1- self & buddy aid; echelon 2- combat lifesaver; echelon 3- Medical specialist). Procedures taught will be according to the American College of Surgeons (ACS) Committee's Advanced Trauma Life Support Course. Initial assessment and management of specific types of injuries are presented to the student through lecture and slide presentations and a written examination. Students who successfully complete lecture and examination requirements, then rotate through animal laboratories associated with the lecture content previously presented. The animal laboratory allows the student to observe and practice to proficiency those life-saving skills necessary in the initial management and stabilization of the trauma patient. The animal laboratory is approximately 2-3 hours per cycle. Each animal station will consist of one instructor and no more than four to five students.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: A total of 18 combat medics and physician's assistants completed the ATLS training program under this protocol in FY94. After action reports and critiques indicated that this training was very well received and judged as extremely valuable in familiarizing emergency Medical personnel in actual hands-on life saving techniques.

PI changed from 1LT Vega to LTC Richard Harris, Chief, Biological Research Service since this a training protocol.

DEPARTMENT OF CLINICAL INVESTIGATION

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): LTC Richard A. Harris

PROTOCOL TITLE: Advanced Laparoscopic Training Procedures for Health Care Providers Utilizing the Porcine Model

PROTOCOL #95/31A STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): K McLarty, LH Senter, J Holcomb, J Szigeti

Keywords: Surgery, laparoscopic, procine

Study Objective: Currently available non-animal models for laparoscopic procedures do not create the texture, bleeding, and handling characteristics of living tissues. Laparoscopic approaches and procedures are being developed and perfected for surgical procedures that are currently performed open. The procedures must be evaluated and performed in living tissues prior to use in humans so that the surgeon can accurately determine how specific tissues and the patient will respond to the manipulations performed. The surgeon must be aware of all possible effects this procedure might have on tissue, such as hemorrhage and tissue damage. Synthetic tissues are not adequate for complete evaluation of surgical procedures prior to implementation in humans. This training protocol is designed to train surgeons in various laparoscopic procedures, using state-of-the-art instrumentation, prior to application to human patients.

Technical Approach: Laparoscopic surgery, or "band-aid surgery," is becoming more and more common. Many times an ordinary surgery requiring a 1-2 week stay in a hospital with a painful recovery can be done by "band-aid surgery" within a single day with no time in the hospital. Oftentimes the patient has little or any pain and is allowed to resume work the day after the surgery. The cost of the hospital bill is greatly reduced. Unfortunately, the surgeon who performs the "band-aid surgery" must develop special skills to learn the right way to handle the instruments. The first part of this training is with non-living objects such as cardboard boxes and plastic dummies. The final portion of the training must be on a living body. Fully anesthetized pigs are used as final training in many procedures that the surgeon will next do on human patients. Many times, only one pig is needed since basic skills were learned on non-living objects. In all cases, the pigs are the fewest number needed and maximum use of the pig is guaranteed by many procedures on a single animal.

Progress: This protocol has proceeded as planned during FY96. Funding and equipment donations from the Ethicon Endo-Surgical Corporation have introduced 16 WBAMC and local surgeons to the latest innovations in laparoscopic equipment and the harmonic scalpel. Established laparoscopic techniques in gynecological surgery have been the focus of training for 9 OB-GYN WBAMC residents. A total of 16 pigs were utilized in this protocol in FY96. The Department of OB-GYN has incorporated training under this protocol as a regular part of their residency program. Overall, training on this protocol has been judged to be excellent with projections from WBAMC physicians and the Ethicon Endo-Surgical Corporation to increase their usage.

DEPARTMENT OF CLINICAL INVESTIGATION

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ William Nauschuetz

PROTOCOL TITLE: Use of High Technology to Determine Risk of Drug-Resistant Tuberculosis in the El Paso Region

PROTOCOL #93/46 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): N Olisa

Key Words: Drug-Resistant Tuberculosis El Paso, Gene Amplification

Study Objective: Short Range Goals

Mobilize key Medical treatment facilities within the El Paso region to recognize the threat of TB and MDRTB: We have already accomplished this goal. The Dept. of Clinical Investigation, WBAMC has agreements with the El Paso City/County Health District and with the El Paso Managed Health Care Consortium (representing four academic institutions and three Medical centers) to address the threat of TB and MDRTB in the El Paso region.

Introduce Polymerase Chain Reaction (PCR) technology for the identification of *M. tuberculosis* and MDRTB: The Dept. of Clinical Investigation, WBAMC is cooperatively working with the El Paso City/County Health District to investigate the sensitivity of PCR compared to routine TB culture and susceptibilities for the detection of *M. tuberculosis* and MDRTB. We also have an agreement with members of the El Paso Managed Health Care Consortium to share clinical specimens to compare PCR with routine TB culture and susceptibilities.

Intermediate Range Goals

Establish the rate of TB and MDRTB for a stable population in Juarez and for Mexican nationals being treated in El Paso Medical centers: Clinical specimens submitted to Medical facilities in Juarez for the diagnosis of TB are stained for the presence of acid-fast bacilli. Those specimens that are AFB smear positive are transported to the El Paso City/County Health District for culture confirmation and antimicrobial susceptibilities. However, the sensitivity of AFB smears is about 50%, so many citizens in Juarez are not laboratory-diagnosed properly. By choosing a stable population within Juarez and doing a sweep collection, we can determine the incidence of TB and MDRTB by performing routine culture on all specimens, despite smear results, and by running PCR on each specimen submitted. The PCR should provide a more sensitive method of detecting latent and subclinical TB. We would also use PCR for TB and MDRTB on all Mexican nationals admitted to El Paso Medical centers showing respiratory symptoms.

Long Range Goals

The data derived from this study can be used to establish the El Paso region as a high-risk area for TB and MDRTB and as an area that has fulfilled the CDC Task Force Guidelines of implementing high technology for the rapid detection of TB and MDRTB. The data can then be used as a baseline for efficacy studies of newer generation antimycobacterial agents, including those requiring shorter periods of treatment.

Technical Approach: This study is triphasic. In Phase I, primers specific for the amplification of IS6110 will be used for PCR amplification of *M. tuberculosis*. The primers will be evaluated on ATCC strains of mycobacterial species. If the primers amplify a specific sequence, Phase II will then compare the detection of PCR-amplified *M. tuberculosis* DNA with standard mycobacteriologic isolation and identification procedures. In Phase III, we will use a primer set that specifically amplifies a 411 base pair sequence from the RNA polymerase gene (*rpoB*) of *M. tuberculosis*. Amplification will be done only on pure growth from routine mycobacteriologic media. The 411 base pair fragment that occurs as a result of the amplification will be sent to Dr. Tryon's laboratory at UT-Health Science Center at San Antonio. He will sequence the fragment and determine if mutations indicative of rifampin-resistance are present in the sequence.

Progress: This study has been terminated both principal investigator and associate investigator have left the institution.

DEPARTMENT OF CLINICAL INVESTIGATION

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): Bruce C. Veit, PhD

PROTOCOL TITLE: Growth Dynamics of Breast Cancer Cells: A Study of Growth Regulatory Factors

PROTOCOL #93/04 STATUS: Completed

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): None

apoptosis, cell lines, breast cancer, cell cycle, flow cytometry, digital image analysis

Study Objective: The aim of this project is to study the biological properties of breast cancer cells as they relate to intra- and extra-cellular growth factor signaling, cell cycle progression, and mutational changes which occur during tumor cell growth as the result of growth factor and chemotherapeutic influence. Information gained from this study should provide a better understanding of the mechanism(s) of breast tumor cell resistance and a rationale for applying appropriate therapeutic methods to the treatment of breast cancer.

Technical Approach: The proposed research program consists of three approaches:

(1) Study of in vitro cultured breast cancer cell lines which express a variety of growth factor receptors, tumor associated antigens and tumor suppressor genes or proto-oncogenes for (a) outgrowth of mutant clones as a function of selective pressure by chemotherapeutic agents, growth factors and cytokines; (b) responsiveness to a variety of growth factors and mitogens; (c) altered expression of cell-surface antigens; and (d) changes in ploidy, S-phase fraction, nuclear antigen expression, and cell cycle variations.

(2) Study of primary isolates of breast tumors (benign and malignant) from patients upon initial diagnosis and at relapse for (a) cellular content of tumor cells, stromal cells, and infiltrating cells (i.e., lymphocytes, monocytes, etc); use of flow cytometry on single-cell suspensions and immuno-histochemical/immunofluorescence image analysis on tissue sections and (b) tumor cell heterogeneity with respect to tumor-associated antigens, growth factor receptors, DNA content (ploidy, S-phase fraction) and cell-cycle variations.

(3) Study primary isolates of malignant breast tumors (at initial diagnosis and at relapse) in vivo in nu/nu mouse xenografts for (a) growth response and selective pressure of chemotherapeutic agents, growth factors and cytokines; (b) alterations in cellular content of tumor cells, stromal cells and infiltrating cells during growth progression and modification through the use of growth factors, chemotherapeutic agents and cytokines; (c) emergence of chemotherapeutically resistant tumor cells and their characterization with respect to growth factor responsiveness; and (d) mechanisms of tumor cell death: use of agents (growth factors or inhibitors) which induce cells to enter cycle or inhibit them from entering cycle in combination with chemo-cytotoxic agents to determine whether cell death occurs via apoptosis or as the result of increased susceptibility during cell cycle.

Progress: Primary human breast cancer tissues obtained from biopsies or mastectomies were characterized for DNA content by flow cytometric and digital image analyses and for expression of growth factor receptors, e.g. estrogen and progesterone receptors. One biopsy was accompanied by an axillary lymph node which contained metastatic tumor. The primary (breast) tumor was observed to contain two aneuploid stem lines with DNA indices of 1.4 and 1.9 and S-phase fractions of 19.8% and 7.4%, respectively. Metastatic tumor contained only one aneuploid stem line with an S-phase fraction 9.6% and had a DNA index of 1.7 suggesting the possibility of emergence of a sub-line in the metastatic tumor.
In future studies, we will focus on the use of DNA analysis and breast cancer-associated markers (e.g., ER, PR, c-erb-B, adhesion molecules) to characterize primary and metastatic tumors for possible emergence of aneuploid sub-lines.

Results of flow cytometric analysis of mutant p53 expression in cell cycle compartments of BT-474, DU-4475 and SK-BR3 cells at various times during a 7-day growth period indicated that, regardless of time in culture and cell cycle compartment, almost all BT-474 cells continually expressed mutant p53 gene product suggesting that constitutive expression of mutant p53 protein in this cell line is not modulated during growth. By contrast, DU-4475 and SK-BR3 cells exhibited marked variations in mutant p53 expression during growth. DU-4475 cells exhibited an increase to 80 - 90% p53+ cells in all three cycle compartments after 1 day and then decreased to 18% p53+ cells by day 7. SK-BR3 cultures which had 41% mutant p53+ cells on day 0 underwent an increase to 98.3% p53+ cells by day 1 and remained at that level through day 7. Since p53 protein is involved in the induction of apoptosis during growth factor deprivation, future studies will be focused on how variable expression of mutant p53 in these three cell lines affects induction of apoptosis.

We have established a model system for studying the involvement of apoptosis in breast cancer cell death. To quantitate apoptotic cells, a DNA 3'-OH digoxigenin-nucleotide end extension - FITC-anti-digoxigenin labeling technique for detecting the presence of fragmented DNA in intact cell nuclei was used. Three breast cancer cell lines were subjected to a variety of different agents that have been reported to induce apoptosis (hyperthermia, TNF-a, camptothecin, and etoposide). Results of these studies indicated that the end-labeling method was capable of detecting apoptosis under conditions where apoptosis has been detected by other methods.

Percentages of apoptotic BT-474 and MCF-7 cells increased significantly in etoposide-treated cultures during a 3-day incubation period. Peak numbers of apoptotic cells occurred at approximately 20 to 30 hours of culture with a significant decline thereafter. Apoptotic cells were distributed unequally among G0/G1, S and G2/M cell cycle compartments with the highest number observed in the S-phase compartment. Whereas numbers of apoptotic S-phase cells decreased after 23 to 30 hours of incubation, G0/G1 and G2/M apoptotic cells remained at constant levels throughout the remainder of culture. These findings are consistent with the S-phase-associated mode of action of topoisomerase inhibitors which primarily affect cells undergoing DNA synthesis.

Since extramural funding for this project had terminated October 95, no further studies have been conducted during 1996.

DEPARTMENT OF CLINICAL INVESTIGATION

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): Bruce C. Veit, PhD

PROTOCOL TITLE: Growth Dynamics of Breast Cancer Cells: A Study of Growth Regulatory Factors using the Murine Model

PROTOCOL #93/05A STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): K Nauschuetz

Key Words: Athymic Mice, Nude Mice, Xenograft, Breast Cancer

Study Objective: The aim of this project is to study the biological properties of breast cancer cells as they relate to intra- and extra-cellular growth factor signaling, cell cycle progression, and mutational changes which occur during tumor cell growth as the result of growth factor and chemotherapeutic influence. Information gained from this study should provide a better understanding of the mechanisms of breast tumor cell resistance and a rationale for applying appropriate therapeutic methods to the treatment of breast cancer. Our studies will attempt to answer the following questions: (1) What are the phenotypic and biological characteristics of variant sublines within breast cancers? (2) Do human breast tumors that grow in thymic nude (nu/nu) mice retain their histological grade and variant subline profiles? (3) What are the selective pressures which create heterogeneity in breast cancers? (4) Do breast cancer relapses occur because of physiological (non-genetic) or mutational (genetic) alterations in growth factor signaling pathways? (5) Do normal stromal cells exert growth regulatory influences on tumor cells via growth factor secretion and/or cytokine production? (6) Does growth factor deprivation of growth factor-dependent tumor cells result in the initiation of apoptosis?

Technical Approach: The proposed research program consists of three approaches:

(1) Study of in vitro cultured breast cancer cell lines which express a variety of growth factor receptors, tumor-associated antigens and tumor suppressor genes or proto-oncogenes for (a) outgrowth of mutant clones as a function of selective pressure by chemo-therapeutic agents, growth factors and cytokines; (b) responsiveness to a variety of growth factors and mitogens; (c) altered expression of cell-surface antigens; (d) changes in ploidy, S-phase fraction, nuclear antigen expression, and cell cycle variations.

(2) Study of primary isolates of breast tumors (benign and malignant) from patients upon initial diagnosis and at relapse for (a) cellular content of tumor cells, stromal cells, and infiltrating cells (i.e., lymphocytes, monocytes, etc.); use of flow cytometry on single-cell suspensions and immunohistochemical/immunofluorescence image analysis on tissue sections and (b) tumor cell heterogeneity with respect to tumor-associated antigens, growth factor receptors, DNA content (ploidy, S-phase fraction) and cell-cycle variations.

(3) Study primary isolates of malignant breast tumors (at initial diagnosis and at relapse) in vivo in nu/nu mouse xenografts for (a) growth response and selective pressure of chemotherapeutic agents, growth factors and cytokines; (b) alterations in cellular content of

tumor cells, stromal cells and infiltrating cells during growth progression and modification through the use of growth factors, chemotherapeutic agents and cytokines; (c) emergence of chemotherapeutically resistant tumor cells and their characterization with respect to growth factor responsiveness; (d) mechanisms of tumor cell death: use of agents (growth factors or inhibitors) which induce cells to enter cycle or inhibit them from entering cycle in combination with chemo-cytotoxic agents to determine whether cell death occurs via apoptosis or as the result of increased susceptibility during cell cycle.

Progress: Fresh primary human breast tumor biopsy tissues were implanted subcutaneously into the mammary fat pads of nude (athymic) mice. None of the transplanted tissues developed tumors in xenografted mice. In some cases, tumors did not grow because the implants were subsequently found to contain either fatty tissue or normal epithelial tissue. In other cases, it is likely that xenograft failures (later determined to involve estrogen receptor+ tissues) were due to the lack of a suitable estrogen-enriched environment (recipient mice were not pre-treated with estrogen). Estrogen supplementation enhances tumorigenicity somewhat but much greater tumorigenicity can be obtained when breast cancer cells are co-inoculated with estrogen and basement membrane matrix. In future attempts to grow xenografted primary breast cancer tissue, we will incorporate this alternative approach.

We were successful in growing two established breast cancer cell lines, BT-474 and DU-4475, as tumor xenografts in nude mice. It is likely that our success rate in growing xenografted breast cancer cells from established cells lines will also increase when we combine the cell implants with estrogen and basement membrane matrix. Because of failures in our early attempts to grow primary human breast cancer xenografts in nude mice and because of the lack of extramural funding (which ended October 1994) to continue this aspect of our studies, we suspended further work in this area and focused our attention primarily on in vitro studies of breast cancer cell lines and the detection of drug-induced apoptosis. Due to lack of continued funding during 1996, no further in vivo studies were conducted and therefore no new results are reportable. This protocol has been terminated due to lack of funding.

DEPARTMENT OF CLINICAL INVESTIGATION

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): COL Idelle M. Weisman

PROTOCOL TITLE: Comparison of Physiologic Responses to Prolonged Exercise Simulating Army Field Training in Sickle Cell Trait and Controls (Phase IVa)

PROTOCOL #88/38 STATUS: Completed

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): RJ Zeballos, J Little, TW Martin

Key Words: Sickle cell trait, Endurance exercise

Study Objective:

1. To determine if submaximal (50-70% VO2 max) prolonged treadmill exercise (1 hour 30 minutes) with a final maximum exercise (5 minutes), similar to Army field training conditions, would elicit differences in exercise performance between Sickle Cell Trait (SCT) and control volunteers.
2. To evaluate changes in Percent Sickling (%S) and blood viscosity with prolonged exercise in SCT volunteers and to analyze their relationship to venous oxygen saturation, hydration status and temperature.
3. To assess biochemical and enzymatic changes in blood and urine that would suggest muscle damage (rhabdomyolysis) during prolonged exercise.
4. To compare the effect of prolonged exercise on renal function in SCT and controls.
5. To determine whether subtle pulmonary microcirculatory abnormalities not present at rest would be detected during exercise in SCT compared to controls.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: This protocol was completed in FY96 with no adverse reactions reported to date. 45 subjects were entered in this protocol. Important papers are currently being written on many different aspects of this study.

DEPARTMENT OF CLINICAL INVESTIGATION

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): COL Idelle M. Weisman

[redacted]

PROTOCOL #93/34 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): RJ Zeballos

Key Words: Anaerobic Exercise, AIT Anaerobic

Study Objective:

(1) To measure the anaerobic power for lower and upper body exercise in male and female soldiers, and develop a data base that may be used as a reference to gauge performance levels of anaerobic power.

(2) To determine the impact of intense anaerobic work on cardiopulmonary functions.

Specific Objectives:

- To determine if the U.S. soldier is more fit to perform anaerobic exercise using upper or lower body exercise.
- To compare the level of anaerobic power of female with male soldiers.

DEPARTMENT OF CLINICAL INVESTIGATION

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): COL Idelle M. Weisman

PROTOCOL TITLE: A Randomized, Double-Blind, Double-Dummy, Comparative Clinical Trial of Tweleve Week Courses of Salmeterol Xinafoate Versus Ipratropium Bromide Versus Placebo (PRN Ventolin®) in Subjects with Chronic Obstructive Pulmonary Disease

PROTOCOL #95/27 STATUS: Completed

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): RJ Zeballos

Keywords: Salmeterol, Comparison, COPD

Study Objective:

Salmeterol xinafoate is a selective long-lasting inhaled beta$_2$-adrenoreceptor agonist for the maintenance treatment of reversible airways obstruction and the prevention of bronchospasm. Salmeterol has been shown to maintain lung function in excess of 20% above baseline for at least 12 hours, with peak increases in lung function equivalent to Ventolin®[15-17]. Chronic dosing studies have shown salmeterol is the optimum dosing regimen for subjects with mild to moderate reversible airway obstruction and is more efficacious than Ventolin®[18.19].

Atrovent (ipratropium bromide) is an anticholinergic (parasympathetic) agent that is indicated for maintainance treatment of bronchospasm assocaited with COPD, including chronic bronchitis and emphysema.

The goals of the study are:

1. To compare the efficacy of salmeterol treatment with that of ipratropium bromide treatment and placebo (prn Ventolin®) in subjects with COPD as measured by BDI/TDI Dyspnea scale, FEV_1 AUC, exercise test and Borg dyspnea assessment, 12 hour PFTs, daily AM and PM peak flow measurements, self-rating of symptoms, nighttime awakenings due to respiratory symptoms, supplemental Ventolin® use and exacerbation rates.
2. To compare the safety of salmeterol treatment with that of ipratropium bromide treatment and placebo (prn Ventolin®) in subjects with COPD as measured by vital signs, clinical laboratory results, 12-lead ECG, clinical adverse events, Medical history, physical exam, chest radiograph and 24-hour Holter recording.
3. To compare the effectiveness of salmeterol xinafoate (42 mcg BID, by inhalation) versus ipratropium bromide (36 mcg QID, by inhalation) versus placebo for reducing subject-perceived sleep quality impairments (as measured by the Pittsburgh Sleep Quality Index (PSQI) scores).

Technical Approach: Multicenter, Stratified, Randomized, Double-blind, Double-dummy study.

Progress: 13 patients were entered in this study. 1 patient withdrew early in the study - medicine was not helping. Adverse reaction on 1 patient was reported to the IRB. We had

12 evaluable cases for this study. Several abstracts from this multicenter (25) study of >400 patients will be presented at the National American Thoracic Society meeting in May 1997. Amendment 1: 14 Mar 95; Amendment 2: 10 May 95 Estimated completion date has changed from Jan 96 to May 96.

DEPARTMENT OF CLINICAL INVESTIGATION

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): COL Idelle M. Weisman

PROTOCOL TITLE: Impact of Smoking on Aerobic and Aerobic Performance During Upper and Lower Body Exercise in Female Soldiers

PROTOCOL #95/06 STATUS: Completed

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): RJ Zeballos, MAJ Kevin Kumke

Keywords: Aerobic, Anaerobic Exercise Performance, Upper Body, Lower Body, Females

Study Objective:

1- To establish a comprehensive quantitative data base of aerobic (exercise longer than 5 minutes) and anaerobic (short bursts of high intensity exercise levels of fitness for female Army personnel for lower and upper body exercise.

2 - To determine if female soldiers are more fit to perform aerobic or anaerobic exercise and upper or lower body exercise.

3 - To correlate upper and lower body levels of fitness with Army Physical Fitness Test results.

4 - To determine the chronic and acute effects of smoking on aerobic and anaerobic performance during lower and upper body exercise.

Study Design: Prospective controlled study to obtain the data base of exercise performance of female soldiers; parallel design, smokers vs. controls to determine the chronic effect of smoking. The same smokers will also be used as their own control to evaluate the acute effect of smoking.

Progress: This study was completed on July 96. 26 patients entered with no adverse reactions reported.

Abstract on next page.

DEPARTMENT OF CLINICAL INVESTIGATION

$\Delta VO_2/\Delta WR$ during Cycle and Arm Crank Ergometry in Women

S. M. Connery, R. J. Zeballos, A. E. Pusateri, M. B Taylor, I M. Weisman

The $\Delta VO_2/\Delta WR$ during incremental cycle exercise testing has been postulated to be a useful marker of cardiovascular dysfunction. Although some conflicting evidence exits (Eur J Appl

DEPARTMENT OF CLINICAL INVESTIGATION

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): COL Idelle M. Weisman

PROTOCOL TITLE: The Assessment of Sputum Properties to Evaluate the Efficacy of Gelsolin in Patients with Chronic Bronchitis: A Pilot Study

PROTOCOL #96/24 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): BK Rubn, RJ Zeballos

Keywords: Chronic Bronchitis, Sputum producivity, Gelsolin

Study Objective: The goals of this pilot study are to evaluate changes in chronic bronchitis sputum after gelsolin treatment in vitro and to determine if these changes are similar to those seen when treating sputum from patients with CF.

Technical Approach: This study proposes to undertake the in vitro dose dependent and time dependent efficacy of gelsolin on the physical and transport properties of expectorated CB sputum. In this stud gelsolin will be compared with rhDNase (positive control) and with gelsolin excipient (negative control). In studies emphasizing spinnability, mucociliary clearability and cough clearability we will assess potential synergy between the effects of gelsolin and rhDNase. We also propose a laser-scanning confocal microscopic analysis of the actin and DNA filament length, configuration and concentration in response to gelsolin in CB sputum in vitro as correlated with changes in the sputum viscoelasticity and clearability. We will use confocal laser scanning microscopy to further quantify how these fiber characteristics change with gelsolin and rhDNase treatment.

Progress: No patients have been enrolled in this study.

DEPARTMENT OF CLINICAL INVESTIGATION

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): COL Idelle M. Weisman

PROTOCOL TITLE: A Phase II Multicenter Efficacy, Safety and Dose-Effect Study of the Expectorant Activity of Oral N-Acetylcysteine in Patients with Stable Chronic Bronchitis

PROTOCOL #96/34 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): RJ Zeballos, KM Kumke, HW Hughes, J Bradley

Keywords: N-Acetylcysteine, Expectorants, Quality of Life, Sputum Effects

Study Objective: To evaluate the mucokinetic activity of three different oral doses of N-acetylcysteine (NAC) and a placebo for their effects on mucus rheology; To evaluate the relationships between mucus rheology, pulmonary gas trapping, exercise capacity and symptomology; To evaluate the effects of three different oral doses of NAC and placebo on symptomology and exacerbation rate in chronic bronchitis. To evaluate the effects of three different oral doses of NAC and a placebo on patient safety.

Technical Approach: Randomized Single-blind placebo run-in, then placebo-controlled, double-blinded parallel group dose-ranging, ten investigational sites (U.S.)

Progress: One patient has been entered to date.

Adverse event was reported by Dr. Weisman on a patient, age 64 was admitted to hospital for surgery of 8 cm abdominal aneurysm. The aneurysm was an incidental finding after COL Weisman ordered a CT scan to follow up on serial changes noted in the screening chest X-ray. Patient was immediately terminated from protocol.

It has been difficult to recruit for this protocol because of the requirements for sputum productivity.

Estimated completion date has changed to Dec 97.

DEPARTMENT OF CLINICAL INVESTIGATION

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): CPT John B. Westover, DVM

PROTOCOL TITLE: Gene Amplification as a Tool for the Rapid and Direct Diagnosis of *Mycobacterium bovis* and *Mycobacterium tuberculosis* in Dairy Cattle

PROTOCOL #94/44A STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): WF Nauschuetz, S Mahlen, SD Pillai

Key Words: Mycobacterium Tuberculosis, Mycobacterium Tuberculosis

Study Objective: The purpose of this study will be to demonstrate the presence of *M. bovis* and *M. tuberculosis* in nasal swabs and milk samples from dairy cattle, as well as sputum samples from humans. A rapid diagnostic test for mammalian *Mycobacterium* species utilizing quantitative PCR techniques is to be evaluated as the primary objective for this project.

The study proposes to introduce the Polymerase Chain Reaction (PCR) technology for the identification of *M. tuberculosis* and *M. bovis*. Veterinary Services, APHIS, USDA will participate in a joint investigation with the Department of Clinical Investigation, WBAMC an and the El Paso City/County Health District to investigate the sensitivity of PCR compared to routine TB culture and susceptibilities for the detection of *M. tuberculosis* and *M. bovis*. The principal investigators are working towards an agreement with management from TB quarantined dairies in Texas and dairies at risk for the infection in Chihuahua, Mexico to acquire clinical specimens for PCR and TB culture evaluation.

The data derived from this study can be used to evaluate and establish the El Paso-Juarez region as a high-risk area for bovine and human forms of tuberculosis, and provide some insight on the dynamics of *M. tuberculosis* and *M. bovis* in human and livestock populations. The implementation of the PCR amplification techniques for the rapid detection of TB is to be evaluated for field application in an endemic region.

Technical Approach: Amplification of the IS6110 sequence in *M. bovis* and *M. tuberculosis* will be optimized with primers IS1 (5'- CCTCGCAG CGTAGGCGTCGG-3') and IS2 (5'-CTCGTCCAGCGCCGCTTCGG-3'). These primers will be used to amplify DNA from an ATCC strain of *M. tuberculosis* (Eisenach, 1991). Amplifications will be run on the Perkin-Elmer 9600. The amplification cycle will be 95^{o}C, 65^{o}C and 72^{o}C. Length, and number, of cycles will be determined during optimization.

The presence of amplified mycobacterial DNA will be detected by electrochemiluminescence using the automated Perkin-Elmer QPCR 5000. Amplified DNA will be hybridized to the specific detection probe (5'-CTGCCCAGGTCGACACAT-3').

DESCRIPTION OF PROCEDURES, TECHNIQUES, OR TESTS: Specimen material, in the form of nasal swabs and milk samples, will be collected from cattle maintained at local commercial dairies. Microbial determination for *M. bovis* and *M. tuberculosis* will consist of standard PCR amplification procedures conducted within the Department of Clinical Investigations, with histopathologic and bacterial culture techniques performed within the Department of Pathology. No surgical procedures or invasive techniques are to be utilized as a result of this protocol.

Progress: This study has been administratively terminated no response has been received from the PI for two years.

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Robert Gerhardt

PROTOCOL TITLE: Evaluation of The Effect of a Cathartic Agent on Gastrointestinal Decontamination With and Without Activated Charcoal: A Clinical Trial

PROTOCOL #96/28 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): D Gerhardt, J Buchannan, W Hartman, AE Pusateri

Keywords: Toxicology, Decontamination, Sorbitol, Carthartics

Study Objective: The study is designed to determine the effect of the cathartic agent sorbitol upon gastrointestinal absorption of a supratherapeutic oral ingestion of acetaminophen (APAP), when used alone and in conjunction with activated charcoal, a chemical adsorbant.

Technical Approach: Prospective, randomized, double-blinded and placebo controlled crossover study.

Progress: Protocol has not started, an amendment was submitted at the Dec 96 IRB meeting.

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DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): COL Michael G. Donovan

PROTOCOL TITLE: Bone-Anchored Craniofacial Prostheses Investigation

PROTOCOL #89/37 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): J Gary, N Dickerson

Implants, Bone-anchored Prostheses

Study Objective:

1. To evaluate the long term retention success rate for titanium implants anchoring craniofacial prostheses.
2. To evaluate the long term stability of the prostheses.

Technical Approach: Patients will be admitted to Ward 6W, and have the routine pre-surgery laboratory studies, to include blood work, x-rays and urinalysis, and any further tests required that would be dictated by their medical history. Appropriate referrals will be given to various medical specialties if indicated. The surgery to implant the prosthesis will be conducted in the operating room. Anesthetic will be given to minimize the pain that is associated with any surgical procedure. The doctor will cut the skin covering the area to be treated and then drill holes in the bones of the face, head, or both. Next, tiny titanium fixtures will be inserted into the holes, the skin will be replaced so that it covers the fixtures, and the skin stitched. The titanium fixtures will be left in place for 3-4 months to allow them to become integrated with the bone. During this time the patient will visit the doctor 2-3 more times so their condition can be monitored.

After 3-4 months, the patient will once again be admitted to the hospital, where they will undergo additional surgery. After the anesthetic is administered, the doctor will again cut the skin covering the area being treated. Some of the tissue under the skin will be removed and the skin will be stitched back together. The doctor will then puncture the skin directly over each implanted titanium fixture and will attach a small skin-penetrating abutment to each fixture. For 3-4 weeks, the treated area will be allowed to heal. During that time the patient will visit their physician 1-3 times so that their condition can be monitored.

After 3-4 weeks, a prosthesis will be made and will be attached to the anchors. After the prosthesis is in place, the patient will continue to visit their physician 3 times during the first year, then twice a year, so that their condition can be monitored, as well as their level of satisfaction.

Progress: This study has been terminated. Principal investigator is deceased. Associate investigator is now out of the Army. 50% of miniature swine used in start of project were infected thus giving questionable results.

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): COL John C. Mitchell

PROTOCOL TITLE: Autologous Pericranium for Temporomandibular Joint Disc Replacement in Sheep

PROTOCOL #93/33A STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): MG Donovan, NC Dickerson

Key Words: Temporomandibular Joint, Reconstruction, Discectomy

Study Objective:

1. Determine the success of autologous pericranium as a temporomandibular joint disc replacement tissue utilizing histological assessments of the morphological changes of the pericranium at timed intervals.

2. Compare condylar morphological changes in temporomandibular joints repaired with pericranial grafts and joints in which unrepaired discectomies are performed.

Technical Approach:

1. Fifteen domestic sheep will be used for this study. A control for a normal temporomandibular joint disc and condyle have been previously studied histologically.

2. Under general anesthesia, each of the fifteen sheep will have autologous pericranium harvested via a biocoronal flap. An incision over the zygomatic arch and glenoid fossa will give access to the temporomandibular joint space. The TMJ discs will be excised bilaterally and the pericranium sutured to the anterior and posterior stumps of the TMJ disc attachments with non resorbable sutures unilaterally. The other temporomandibular joint will go unrepaired following its discectomy.

3. Three sheep will be euthanatized at one month, two months, four months, six months, and ten months to obtain specimens for histological studies.

4. The pericranium from each joint site will be studied for histological changes and fibrous adhesions.

5. The condyles of each animal will be studied to assess any changes as a result of the autologous pericranium TMJ disc replacement. These will be evaluated radiographically and by histological sections.

Progress: The resident responsible for postmortem specimens has PCS'd twice since the start of the protocol. Data is irretrievable.

DEPARTMENT OF MEDICINE

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jennifer L. Cadiz

PROTOCOL TITLE: Resectable Bronchogenic Carcinoma: Value of Routine Contrast - Enhance Cranial MRI in Preoperative Staging

PROTOCOL #95/04 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): JL Wallingford, R Gore, JJ Leech, WM Boushka

Keywords: Bronchogenic cancer, MRI, brain metastases

Study Objective: We propose a collaborative study to examine the incidence of clinically occult brain metastasis in patients with resectable primary bronchogenic carcinoma.

Bronchogenic carcinoma remains the foremost cause of death from cancer in men in the United States and has risen dramatically for women. Since treatment and survival are greatly influenced by the presence of brain metastases, the detection of such lesions would greatly influence survival. The incidence of metastases from lung carcinoma ranges between 17-40% in autopsy series. The brain is frequently the only site of recurrence in patients who have already undergone thoracotomy for non-small cell carcinoma. Clinically silent lesions can occur and most frequently are seen in patients with adenocarcinoma and small cell carcinoma.

Several groups have documented the utility of cranial CT in the preoperative assessment of bronchogenic carcinoma. Between 5-10% of neurologically intact patients undergoing routine CT of the head were found to harbor intracranial metastatic lesions. Contrast enhance MRI is now the acknowledged gold standard for the evaluation of the CNS for metastasis. The superior contrast resolution, lack of ionizing radiation, and lack of potential complication from iodine contrast media used in CT make enhanced-cranial MRI an ideal screening modality for brain metastases.

Technical Approach: Please specify in your own words the basic protocol from Madigan is unclear.

Progress: CPT William M. Boushka, M.D., Chief, MR and CT, Dept of Radiology. Estimated completion date has changed from Nov 96 to Dec 96. Change in PI from MAJ Lynn Keenan to MAJ Jennifer L. Cadiz. No progress was reported by PI for FY96.

DEPARTMENT OF MEDICINE

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jennifer L. Cadiz

PROTOCOL TITLE: Talc Insufflation vs. Minocycline in a Randomized Double Blind Prospective Trial of Intrapleural Therapy for Recurrent Malignant Pleural Effusions Via Thoracoscopic Guidance

PROTOCOL #94/32 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): JL Cadiz, SP Hetz, B Hammacker, P Stanley, GR Ripple

Key Words: Talc vs. Minocycline

Study Objective: To determine the efficacy of minocycline vs. talc insufflation for sclerosis of malignant pleural effusions via thoracoscopic guidance.

Technical Approach: This study follows standard of care for patients with pleural effusion who are scheduled for thoracoscopic pleurodesis. The only deviation involves use of minocycline in the experimental group. We will follow patients from diagnosis through follow-up.

1) The patient with clinically suspected recurrent free flowing malignant pleural effusion by pleural fluid cytology or pleural biopsy will be identified.

2) The patient will undergo chest X-rays, which should show freely flowing pleural fluid or loculated fluid and confirming the lack of mediastinal shift.

3) If the patient meets eligibility criteria, informed consent will be obtained and the patient will be enrolled into the study.

4) A data sheet (see Appendix I) will be kept recording laboratory data, ECOG performance status, and chest radiograph results as well as demographic information: age, sex, institution, diagnosis, stage of disease, type of chemotherapy received, side effects to the sclerosant including: pain, fever, hypotension, allergic reaction, rash (maculopapular or erythematous), fatigue, anorexia, nausea, vomiting, diarrhea, elevated liver function tests, anemia, neutropenia, and elevated blood urea nitrogen or creatinine.

5) Sclerotherapy procedure:

(a) IV sedation with Versed and Morphine sulfate titrated to drowsiness and slurred speech.

(b) After the patient is placed in the lateral decubitus position and the chest is prepped and draped, a 10 mm thoracoport will be introduced into the pleural cavity under local anesthesia. Any loculated fluid will be aspirated and adhesions gently taken down. Then, the randomly selected sclerosant (talc<3 g vs. minocycline 300 mg) will be sprayed into the pleural cavity coating both the visceral and parietal pleura.

(c) After 20 minutes, a chest tube will be inserted and placed on suction, re-expanding the lung.

(d) Suction will be maintained for at least 24 hours and until pleural drainage is less than 150 ml/day. Then the chest tube will be removed.

(e) From the time the sclerosant is injected the patient will receive 650 mg of Tylenol PO every four hours for a total of 48 hours.

6) Chest radiographs will be obtained at 72 hours to assess for recurrence of the effusion after the sclerosis. If the fluid reaccumulates more than 50% of the original volume after sclerosis, the patient will be considered a treatment failure and considered for either no further treatment or surgery.

7) The following labs will be obtained at 24 and 48 hours for monitoring of side effects: complete blood count, liver function tests, blood urea nitrogen and creatinine.

8) The investigators will monitor for the side effects mentioned on the flow sheet during the first 48 hours after the sclerosis has been completed.

9) Assuming the sclerosis is initially successful, chest radiographs will be obtained at 7 days, 14 days, 30 days, 60 days and 90 days to assess for response. Response rates will be defined in the following manner:

(a) Complete response: No fluid present on chest radiograph.

(b) Partial response: asymptomatic pleural fluid equal to less than 50% of the original width at mid thorax measured on the lateral decubitus film.

(c) Treatment failure: recurrence of the pleural effusion greater than 50% of the original width at mid thorax measured on the lateral decubitus film, a loculated pleural effusion which is 50% of its original volume on PA and lateral roentgenograms or a recurrent symptomatic effusion of any size.

(d) All chest roentgenograms enrolled in the study at WBAMC will be read by the same observer, Dr. Ripple.

Progress: Change in PI from MAJ Lynn Keenan to MAJ Jennifer L. Cadiz. No progress was reported for FY96 from PI.

DEPARTMENT OF MEDICINE

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jennifer L. Cadiz

PROTOCOL TITLE: A Double-Blind, Randomized, Phase III, Multicenter Study of Suramin and Hydrocortisone versus Hydrocortisone and Placebo in the Treatment of Patients with Metastatic, Hormone-Refractory Prostate Carcinoma (Stage D2) (Protocol 1003-01)

PROTOCOL #95/32 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): RF Heaven

Keywords: Suramin, prostate cancer chemotherapy

Study Objectives: To evaluate (1) the role of Suramin in the treatment of hormone-refractory metastatic prostate cancer to control pain, improve patients' overall functional status, and decrease the size of, or eliminate, sites of disease and/or improve patient survival, (2) the feasibility of administering Suramin in the community hospital setting, and (3) patient tolerance of side effects of treatment.

Technical Approach: This is a randomized, double-blind study of hydrocortisone with either Suramin or placebo. Patients with progression of disease on the placebo arm will be crossed-over to treatment with Suramin.

Progress: No progress was reported by the principal investigator for FY96.

DEPARTMENT OF MEDICINE

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Timothy Endy

PROTOCOL TITLE: Immunoregulation and Pathogenesis of Symptomatic, Primary HIV-1 Infection

PROTOCOL #94/21 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): ML Robb

Key Words: Immunoregulation, Pathogenesis, HIV-1

Study Objective: The objective of this study will be to determine and follow the genotypic expression of the HIV from the earliest moments of infection and the very specific patient immune response to the evolving genotypic expression. We also hope to characterize viral burden and correlate viral burden with genotypic expression, specific immune responses, and clinical disease. This will be important as it is not known which factors (viral specific or host specific) that lead to the expression of HIV virus during the acute retroviral syndrome and the ability of the host's immune response to at least initially control the viral infection. A better understanding of this mechanism may lead to effective immunotherapeutic approaches to this disease.

The role of the WBAMC PI will be in identifying patients with acute retroviral syndrome and following the patients clinically. WBAMC (the PI) will be responsible for blood drawing and shipment of clinical specimens.

Technical Approach: The study will be prospective, natural history. Details are lengthy and are specified in the original protocol. Copies are on file at DCI.

NOTE: This is a Tri-Service protocol which originated at Walter Reed Army Medicall Center and was approved at the Human Subject Research Review Board meeting in May 93.

Progress: Principal investigator has left WBAMC.

DEPARTMENT OF MEDICINE

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ David Finger

PROTOCOL TITLE: Sjogren's Syndrome In Patients With Interstitial Cystitis

PROTOCOL #96/10 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): None

Keywords: Sjogren's syndrome, cycstitis

Study Objectives: To show whether or not there is an increased association of SS in patients previously diagnosed with IC, and to further determine if certain class II HLA alleles (such as DR3) are present in such patients.

Study design: A cohort of patients previously diagnosed with IC by a urologist will be identified from a retrospective review of medical records, and then prospectively evaluated for the presence of SS by a rheumatologist. Diagnostic criteria for SS will be based on the European Community criteria previously published.

Progress: Ten patients were enrolled into the study, and their evaluation is complete. The final step will be enrolling and evaluating an equal number of control patients (age and sex-matched). This has not been done due to staffing and ancillary support shortages, but I anticipate conclusion by the Spring of 1997.

Twenty percent of the patients with interstitial cystitis (IC) were found to have definite Sjogren's syndrome (SS), 20% were found to have no criteria, and 60% were found to have some objective criteria but not enough for a definitive diagnosis of SS. Though the numbers are small, it is suggestive of an increased association between IC and SS. This study is currently ongoing and will continue through May 97. This study is being done in collaboration with Walter Reed AMC involving 25 IC patients and controls.

DEPARTMENT OF MEDICINE

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): CPT Luis M. Irizarry

PROTOCOL TITLE: The Prevalence and Severity of Band-Keratopathy in Patients with Primary Hyperparathyroidism

PROTOCOL #94/05 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): KJ Simcic, DP Mong, WF Davitt

Key Words: Primary Hyperparathyroidism, Band-Keratopathy

Study Objective: To assess the frequency and severity of BK in patients with PHP. If the frequency of bk is significant in these patients, possible correlations with the duration and or severity of the php will be examined.

Technical Approach: Single center, prospective, single blind case control study.

Progress: There has been 30 subjects entered with no noted adverse reactions. We have now completed eye exams on 22 patients with primary hyperparathyroidism (with an average duration of 8-10 years) and on 8 control patients. We would like to recruit and test a few more control patients before ending the study. The estimated completion date has been changed from June 1994 to March 1995.

Although the study is negative thus far, we feel that our results are still significant. It appears that patients with primary hyperparathyroidism can be permitted to live with their disease untreated for at least 8 -10 years without significant risk of band-keratopathy.

DEPARTMENT OF MEDICINE

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Mark Jarek

PROTOCOL TITLE: Comparison of Triamcinolone Acetonide with Indomethacin in Treatment of Pseudogout

PROTOCOL #95/08 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): KJ Simcic

Keywords: Primary Hyperparathyroidism, Band-Keratopathy

Study Objective: To assess the frequency and severity of BK in patients with PHP. If the frequency of BK is significant in these patients, possible correlations with the duration and or severity of the php will be examined.

Study Design: Single center, prospective, single blind case control study.

Progress: Study terminated.

DEPARTMENT OF MEDICINE

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Albert J. Martins

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo Controlled, Parallel Group Study to Examine Safety, Efficacy and Pharmacokinetics of a 3-Day Loading Plus Maintenance Infusion Regimen of 619C89 Mesylate Injection in the Treatment of Patients with Symptoms of Acute Stroke

PROTOCOL #95/18 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): J Brainman, JM Herrold

Keywords: Stroke

Study Objective: To study 619C89 Mesylate injection given as intravenous loding plus maintenance infusions with reference to safety, efficacy and pharmicokinetics in the treatment of patients with acute stroke. Drug treatment period is 3 days with follow-up to 12 weeks.

Technical Approach:

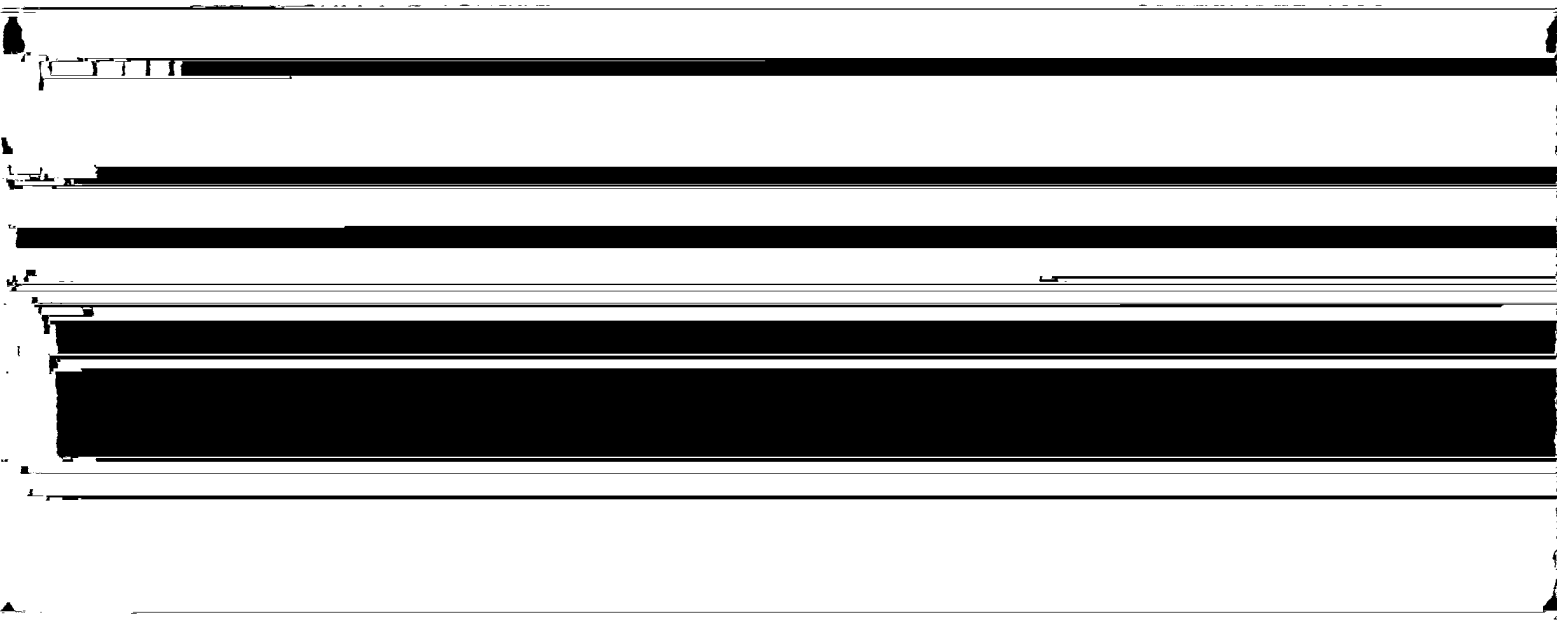
(a) Medicaltion Used. The proposed Phase II study is a randomized, double blind, multicenter three day maintenance and infusion study of the experimental drug Mesylate (Burroughs-Wellcome Drug 619C89, Research Drug Investigation and Development # 46-615) *only* in selected stroke patients presenting to the hospital within 12 hours of ictus. Mesylate in known to block the uncontrolled neurotoxic effects of the above mentioned excitatory neurotransmitters aspartate and glutamate.

(b) Type of Subjects Represented: Rigorous inclusion criteria will be employed to enter a stroke patient into this Protocol 137-103. [See the F.A.C.T. Trial Subject selection section in the Protocol Dated 19 September 94 (Pages 21-22)]. In short, no patient with significant alteration of consciousness or liver or heart disease will be considered a candidate for the study. N.B. No pre-menopausal or unsterilized women will be offered participation in this study.

(c) Number of Patients to be Involved in the Study: The WBAMC, Department of Medicine presently sees approximately four to five stroke patients per month. If one patient per month meets all the inclusion criteria and is entered into this Multi-Centered study, we can hopefully contribute to alleviating the suffering of an untold number of future stroke victims.

Progress: FDA changed protocol and Medical Center involved - after Burroughs-Wellcome and Glaxo united.

DEPARTMENT OF MEDICINE



PRINCIPAL INVESTIGATOR(S): MAJ Megan Mills

PROTOCOL TITLE: Phonophoresis Versus Iontophoresis in the Treatment of Acute Patellar Tendinitis

PROTOCOL #96/18 STATUS: Completed

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): S Morrow, J Burton, K Reilley, P Nagel

Key Words: Patellar Tendinitis

Study Objective:
The purpose of this study is to determine whether iontophoresis or phonophoresis is more effective in the treatment of acute patellar tendinitis.

Technical Approach: Completely randomized design. Subjects will be randomized using a random numbers table (Cochrn and Cox, 1992) in the event that they volunteer for the study. Subjects will be blocked by sex and assigned randomly within blocks to receive 1) iontophoresis, 2) phonophoresis, or 3) control treatments. The control group will receive phonophoresis sham treatments.

Progress: The study began at the CTMC Physical Therapy Clinic in the May-June time frame. To date we only have approximately 5 subjects as many knees we evaluate we didn't meet the research criteria. This lack of subjects is possibly due to the time-frame of the study (summer vs winter) in a season where we don't see a lot of basketball injuries. (Jumpers more commonly get patellar tendinitis).

The study will be completed in November 96 as the associate investigators will be consolidating the information and presenting it as a graduate requirement from PT school in December 96. The principal investigator is planning on being on maternity leave for the last of October and November.

DEPARTMENT OF MEDICINE

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): COL Albert J. Moreno

PROTOCOL TITLE: The Role of Three Phase Bone Scintigraphy in Women with Pelvic Masses

PROTOCOL #95/33 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): J Calson, N Hoshaw, G Maxwell, CE Jimenez, EJ Pacheco

Key Words: Bone Scan, Pelvic Mass

Study Objective: The objective of this study is to perform one bone scan with the anterior pelvis flow and blood pool views in women who are being evaluated in the gynecology clinic for pelvic masses. The bone scan images will be evaluated for the occurrence, size, location, and uptake characteristics of the pelvic mass. The scan would be performed prior to surgical removal of the mass. Other imaging methods, such as ultrasonography, computer tomography, or magnetic resonance imaging will be done to further characterize the pelvic mass if they are needed by the gynecologists.

Technical Approach: The subjects selected for this study will be from patients being evaluated for pelvic masses in the gynecology clinic. A bone scan will be performed on the patients selected for participation in this study. The bone scan will include a flow and immediate blood pool images of the anterior pelvis. The findings on the scan scan will then be correlated with the gynecologic workup which will include pelvic examination, possible ultrasonographic or computer tomography evaluation, and possible laparotomy/laparoscopy. The bone scan findings will be correlated to the pelvic mass in terms of size of the mass, the type of mass, and the location of the mass. The sensitivity of detection of pelvic masses by the three phase bone scan will be determined.

Progress: To date about 40 patients with pelvic masses have been identified and have had bone scans. All appear to have abnormal flow and blood pool images corresponding to the pelvic mass. No comparison of the pelvic pathology and flow/blood pool patterns have been made at this time. No adverse reactions were reported. Estimated completion date has been extended to May 97.

DEPARTMENT OF MEDICINE

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): COL Albert J. Moreno

PROTOCOL TITLE: Diagnostic Adrenal Scanning with 131I (NP59)

PROTOCOL #76/33 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

Key Words: Adrenal Scanning, 1-131 NP 59

Study Objective: To determine the usefulness of ^{131}I-NP59 in scanning of the adrenal glands. This agent will be used (1) as a screening test for detection of primary aldosterone tumor, Cushing's disease, adrenal cortical adenoma, or pheochromocytoma; (2) to image adrenals in patients who require adrenal venography and are allergic to contrast media; (3) to detect unilateral adrenocortical hypofunction - calcification, metastatic carcinoma, post-venography infarction, etc.; (4) to detect functioning adrenal remnant after adrenalectomy for Cushing's syndrome; (5) to aid in assessment of adrenocortical function in patients who have been on adrenocortical steroid therapy.

Technical Approach: Patients with clinical evidence of adrenal disease will be thoroughly evaluated by an endocrinologist. Following intravenous administration of ^{131}I-NP59, adrenal scanning will be performed after 7-10 days. The material will be obtained from the Nuclear Pharmacy, University of Michigan. The WBAMC radiopharmacist will perform sterility and pyrogenicity tests on the radiochemical to ensure that radiopharmaceutical standards are met prior to injection

NOTE: Project was erroneously terminated in Oct 84. Project reactivated in Sep 92 and folder was reconstituted to include required documentation.

Progress: Thirteen patients have been enrolled in this study since this protocol was approved. No adverse effects noted. I-131-NP59 s an adrenal cortical imaging agent produced by the University of Michigan for use as an IND drug. Adrenal cortical imaging is not performed often but when it is, it may reveal hyperplastic adrenal glands or adenomas. Due to the infrequent use of this agent, I-131 NP 59 will probably never come off of investigation status.

DEPARTMENT OF MEDICINE

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): LTC Jeffrey Stiles

PROTOCOL TITLE: A Five-Year Observational Study to Evaluate Clinical Response and Recurrence Rate in the Treatment of Basal Cell Carcinoma with Fluorouracil/Epinephrine Injectable Gel

PROTOCOL #95/38 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): NA

Keywords: Basal Cell Carcinoma, 5 Flourouracil, Therapeutic Implant

Study Objective: This is a phase 3 multicenter clinical trial assessing the efficacy of a Fluorouracil/Epinephrine injectable gel for the treatment of uncomplicated basal cell carcinomas. There are three primary objectives with this protocol

OBJECTIVE 1 - To describe the rate of recurrence of basal cell carcinoma 12 months after treatment in those individuals who demonstrated complete response at Month 3 follow up.

OBJECTIVE 2 - To describe the clinical response rate of treatment with 0.5 ml 5-FU/epi injectable gel when administered 3 times weekly for 2 weeks in patients with uncomplicated basal cell carcinoma.

OBJECTIVE 3 - To evaluate the safety of the fluorouracil/epinephrine injectable gel when administered as directed above.

Technical Approach: Open label study. Approximately 400 patients will have one lesion selected for study. Investigators will use a predetermined randomized schedule to select a target lesion in patients with more than one clinically diagnosed and /or biopsy proven eligible lesion. An analysis of the data will be done when the last patient has completed Follow-up Month 12. Subsequent analysis of annual recurrence rates will be performed.

Progress: Eleven patients have been entered in this study. One patient died of cardiopulmonary arrest, (unrelated to study, data provided in detail to the IRB in Apr 96). One patient was disenrooled because of recurrence of the target basal cell carcinoma (as per study regulations). Nine patiens remain enrolled, no one is in the treatment phase, all are in the follow-up phase with no evidence of recurrence of the basal cell carcinoma. There have been no significant adverse events to date. The nine enrolled patients are happy with the results. Estimated completion date has been extended to Aug 2000.

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): LTC Wellington Sun

PROTOCOL TITLE: Early Diagnosis of Tuberculosis Using Gene Amplification Techniques (GAT)

PROTOCOL #92/65 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): HM Gelston, TJ Casey

Keywords: Polymerase Chain Reaction, Tuberculosis, Gene Amplification

Study Objective: To compare gene amplification techniques with current culture methods in the diagnosis of tuberculosis.

Technical Approach: This protocol will consist of two phases. Phase I will be the validation phase and Phase II will be the prospective evaluation of clinical respiratory specimens. Sources will be consecutive specimens submitted to the WBAMC Mycobacteriology Lab as well as specimens from TB cases submitted to El Paso County Heath Laboratory.

Progress: Principal investigator has left WBAMC.

DEPARTMENT OF MEDICINE

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): LTC Wellington Sun

PROTOCOL TITLE: Comparison of Subcutaneous and Nebulized Trimethoprim-sulfamethoxazole in the Prophylaxis of *Pneumocystis carinii* Pneumonia (PCP) in Rats

PROTOCOL #93/40A STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): RA Harris, TP Baker

Key Words: Pneumocystis, Pneumonia, Trimethoprim, Sulfamethoxazole

Study Objective: To determine if *Pneumocystis* pneumonia can be prophylaxed in rats using nebulized trimethoprim-sulfamethoxazole.

Technical Approach: This will be an animal experiment. Sixty Sprague Dawley rats will be divided into 3 groups of 20 rats. Group I will serve as control and receive nebulized D5W with 1% benzyl alcohol, the vehicle of trimethoporim-sulfamethoxazole. Group 2 will receive nebulized trimethoprim-sulfamethoxazole prophylaxis. Group 3 will receive twice weekly subcutaneous trimethoprim-sulfamethoxazole which has been shown to be 100% effective in preventing PCP in the rat.(25) Each rat will receive the same regimen of oral dexamethasone and tetracycline in the feed on Day 0 as per Hughes.(26) On Day 4 nebulization will be delivered in the same manner to all rats in Groups 1 and 2 using a micronebulizer(Bird Corporation, Palm Springs, Calif). During administration of nebulization the rats will be attached to a plethysmograph to monitor ventilation. Dose administered will be estimated by method as outlined by Girard.(9) Group 3 rats will also receive subcuatneous trimethoprim-sulfamethoxazole on Day 4. Prophylactic drugs will be administered subsequently weekly from Day 4. All rats will be inoculated intra-tracheally with 0.2 ml of a 2 X 10^6 trophozoite/ml solution on Day 6. Two sentinel rats from each group will be euthanized at weeks 2, 4, 5, 6 and 7 to monitor progress of infection. Plasma, lung and liver will be harvested from the sentinels and stored at -70^{o}C to assay for drug levels. All euthanized sentinel rats and any rats dying during the experiment will be examined for evidence of PCP. PCP infection will be determined by special stains of lung tissue and described as either infected or not infected. Severity of infection will be graded according to the number of *Pneumocystis* cysts as per Girard et al.(25) The experiment will last 8 weeks. All rats will be euthanized at that time and assayed for evidence of *Pneumocystis carinii* infection. Serum liver function tests, BUN, creatinine and complete blood count will be done. Liver and lungs will be examined histologically for any evidence of toxicity. Survival will be expressed by Kaplan-Meier plot.

Progress: This study has been administratively terminated, principal investigator has left this institution.

DEPARTMENT OF MEDICINE

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): Patricia A. Frank, RN

PROTOCOL TITLE: RV84: Assessment of Risk Factors for HIV-1 Infection Among Active-Duty U.S. Military Personnel with Documented Recent HIV-Antibody Seroconversion - Phase II

PROTOCOL #94/40 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): AR Morton

Keywords:

Study Objective: To evaluate biological and behavioral determinants of HIV-1 Seroconversion by comparing Medicall, demographics, and behavioral histories of active duty personnel recently infected and/or diagnosed, with HIV-1 histories of individuals who have not seronverted over a similar period of time.

Technical Approach: The study will be conducted by military and civilian personnel (principal investigator, associate investigators and HIV-POC's) in the Army, Navy and Air Force. The sites where we plan to conduct the study have already agreed to participate in Phase II.

Enrolling subjects: A roster of seroconveter cases and matched controls will be provided to each HIV-POC. The roster will contain the name, rank, and unit assignment. Two male controls for each male case and three female controls for each female case should be recruited form the list of eligibles provided. It is the HIV-POC's responsibility to contact potential respondents and to invite these individuals to participate in the study. Recruitment will be conducted in accordance with the information provided on the consent agreement affidavit (enclosure #2). The importance of this study, along with the absolute safeguards to anonymity and confidentiality, should be stressed.

Upon enrollment, a study ID number will be assigned to each participant. This number will be entered into the computerized questionnaire and on the log of study participants (enclosure #5) with the corresponding case/control status of all participating individuals. HIP-POC will also be provided with the interval dates (i.e., last negative - first positive) for each seroconverter case. Interval dates for controls will be the same as their matched case. These dates should be entered into the computerized questionnaire of each participant. Subject's names or other identifiers must not appear on the log or the questionnaire. The log will be kept by the HIV-POC and will be mailed to WRAIR after interviews at the facility have been completed, so that case or control status can be determined for each completed questionnaire.

In addition to the log of study participants, another log (enclosure #6) of eligible cases and controls who decline to participate will be maintained by the HIV-POC. This log will allow for comparison of demographic information between case/control participants and nonparticipants to determine if those who volunteer for the study are different from those who do not, thus indicating the existence of potential study bias.

The HIV-POC must obtain signed consent before cases or controls are interviewed. Consent forms are to kept locally until the end of the study in 1997 and then will be turned over to the principal investigator.

The location and time schedule for interviewing must be flexible and designed for the ease and convenience of study participants. Individuals may wish to complete the computerized interview during duty hours (~0730-1630) or before/after duty hours.

Interviews: In order to minimize response bias, maximize confidentially, and standardize interview procedures, interviews will be conducted using a computer program modeled after the audio computer assisted self-interview system (ACASI) developed by Research Triangle Institute (RTI).(8) With this technology, the computer plays a recorded version of question and answer choices to the respondent over headphones. The participants responds through the keyboard. The computer records the response and, based upon the answer, plays the next appropriate question. A laptop PC, programmed with the questionnaire in ACASI-type format, will be provided to each participating post. (A hard copy of the questionnaire for men and for women is presented at enclosure #7). Prior to beginning each interview, the HIV-POC will explain to the participant the nature of the study and the reason for the interview. Although the participant will have received this information previously from the HIV-POC and will have signed a consent form, the HIV-POC will again describe the study and stress that anonymity will be maintained at all times. The computerized interview will commence only after the HIV-POC is satisfied that the participant understands the procedures and has no questions.

The laptop computers will be stationed in a quiet and private room. Individuals directly associated with recruiting and assigning code numbers to study subjects will never have access to information obtained during the interviews of cases or controls. To ensure total confidentiality of the interview, the responses entered into the computer will be encrypted. This process will make it impossible for anyone to examine the contents of the interview. The decryption key needed to translate the interview record into a usable format will be kept by the investigators at WRAIR.

Progress: This study has been administratively terminated, principal investigator has left this institution.

DEPARTMENT OF MEDICINE

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): CPT Julia Dehoyas

PROTOCOL TITLE: Antihypertensive and Lipid Lowering to Prevent Heart Attack Trial (ALLHAT)

PROTOCOL #94/36 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): L Marcus

Key Words: Hypertensive, Lipid Lowering

Study Objective: This study is a practice-based randomized, clinical trial of antihypertensive pharmacological treatment and, in a specific subset, cholesterol-lowering, in 40,000 high-risk hypertensive trial, including at least 55% African-Americans. The purpose of the antihypertensive trial component is to determine whether the combined incidence of fatal coronary heart disease (CHD) and non-fatal myocardial infarction differs between diuretlogic treatments -- a calcium antagonist (amlodipine), an ACE inhibitor (lisinopril), and an alpha adrenergic blocker (dixazosin). Because of the morbidity and mortality form cardiovascular diseases, and all-causes mortality, the antihypertensive trial component will not include a placebo or no-treatment control group. The purpose of the cholesterol-lowering trial hypercholesterolemic men and women aged 60 years and older with the 3-hydroxymethlglutaryl coenzyme A (HMG CoA) reductase inhibitor pravastatin will reduce all-cause mortality as compared to control group receiving "usual care".

Secondary objectives of both trial components are to compare the effects of their respective treatment regimens on cardiovascular mortality, major morbidity, health costs, and health-related quality of life. Additional secondary objectives of the antihypertensive trial are to compare the effects of alternative treatments on all-cause mortality and on major hypertension-related morbidity such as incidence and regression of left ventricular hypertrophy and progressive renal dysfunction. Additional secondary objectives of the lipid-lowering trial are to assess the long-term safety of HMG CoA reductase inhibitors in men and women aged 60 years and above (particularly with regard to mortality from non-cardiovascular causes), the effect of lipid-lowering on cancer incidence and mortality, and the effect of lipid-lowering on the combined incidence of fatal CHD and non-fatal myocardial infarction, especially in key subgroups (over age 65, women, African Americans, type II diabetics). Also, because this component of the trial will not be blinded, the incidence of myocardial infarction based on centrally coded changes in biennial study ECG will be looked at as an end point. The mean duration of the trial is expected to be 6.0 years, ranging from 5.0 years (for the last patient entered) to 7.5 years (for the first patient entered)

To maximize statistical power for the primary hypothesis of the antihypertensive trial, i.e., the comparison of each alternative drug regimen to diuretic, 1.7 times as many patients will be assigned to its diuretic arm as to each of its other three arms (Table 1). It is anticipated that half of ALLHAT participants will be randomized to both trial components and that half will be randomized only to the antihypertensive trial component.

Technical Approach: ALLHAT will employ an organizational structure that differs markedly from the usual NHLBI-supported clinical trial. The trial will be performed by a large number (250-300) of practicing physician-investigators who will be compensated on a per capita basis for each patient seen according to a fixed payment schedule. Approximately 20% of study

patients are expected to be recruited by the Department of Veterans Affairs (VA) hypertensive clinics.

Progress: Change of investigator in 1995 from Dr. A Quint, to Dr. Julia R. De Hoyos. To date 15 patients have been enrolled. 1 patient withdrew from the WBAMC ALLHAT site but transferred to another ALLHAT center in Florida. 1 patient withdrew from ALLHAT medication due to LE edema, patient remains in study for follow up purposes. This study is estimated to be complete in 2001.

PREVENTIVE MEDICINE SERVICE

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Patricia Kelly, AN

PROTOCOL TITLE: The Efficacy of Nicotine Replacement Therapy Combined with Nurse Counseling and Follow-up

PROTOCOL #96/11 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): BJ Whittemore

Keywords: Tobacco, Cessation

Objectives: The purpose of this study is to demonstrate the efficacy of counseling combined with NRT to produce tobacco cessation in this population.

Study design: This is a retrospective review of existing records which will continue prospectively through 30 September 1996.

Progress: Number of subjects entered to date is 177. Addition of MAJ Becky J. Whittemore, associate investigator.

PREVENTIVE MEDICINE SERVICE

DETAIL SUMMARY SHEET SEPTEMBER 1996

CO-PRINCIPAL INVESTIGATOR(S): Jennifer Schaller-Ayers, AN and
LTC Helena Montano, Ph.D

PROTOCOL TITLE: Beneficiary Health Care Needs Survey

PROTOCOL #96/26 STATUS: Completed

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

Keywords: Health Care System Survey

Study Objectives: This telephone survey research project, Beneficiary Health Care Needs Survey, asks questions of William Beaumont Army Medical Center eligible recipients regarding usage, perceptions and barriers in the health care system. Additionally participants are queried about knowledge and interest in prospective changes in their health care system. Approximately 500 randomly selected households will participate in this project. Data/analysis will be utilized in the upcoming planned change to TRICARE.

Study Design: The study design is survey. The purpose of survey design is to study behaviors as they exist in a target population (Wilson, 1993). The strength of survey research lies in the ability to examine variables within random samples and make conclusions about the target population from the sample data. Survey design is utilized when there is limited knowledge, hypotheses cannot logically be developed from theoretical base, and an independent variable either cannot be manipulated or identified. Representative samples are a requirement of survey research. This design is inherently descriptive (Brink & Wood, 1989).

Progress: This survey was designed by a committee of WBAMC Department Chiefs and administered by UTEP Masters in Nursing students. The survey measured usage, perceptions of our health care delivery system and identified barriers to care at WBAMC.

The major limitation of the study was a small sample population primarily to an outdated HIS system which did not have current phone numbers. The HIS system does not update patient phone numbers with every encounter. Of the 2456 telephone calls made, only 239 beneficiaries were contacted as only 26% of the phone numbers were correct. Of those contacted, most were willing to participate in the study; refusal rates were 6% for AD and 8.6% for Retirees.

As TRICARE approaches, it is important to note that only 19% have some knowledge of it. Also in the new competitive environment that we will face, we must seriously consider why our customers rate Quality as the fourth reason they choose us. This is their perception of quality.

The project was a cooperative community participation effort with reciprocal benefits and I have extended our thanks to UTEP for their assistance in our mission.

DEPARTMENT OF NURSING

DETAIL SUMMARY SHEET SEPTEMBER 1996

CO-PRINCIPAL INVESTIGATOR(S): MAJ (P) Leo F. Voepel
COL (Ret) Thomas A. Beeman

PROTOCOL TITLE: Decay and Reacquisition of Field Medic Knowledge and Skills

PROTOCOL #95/45 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): RA Wisher

Keywords: Field Medic Knowledge

Study Objective: To gauge the proficiency of IRR soldiers completing a rapid train-up of field medic tasks through a comparison with active duty soldiers participating in medical proficiency training.

Technical Approach: A 72-item knowledge test will be given before and after the military proficiency training. Half of the students will complete one form of the test, the other half of the student will complete a different form of the test before the training. The opposite version of the test will be given to the students after the training. A hands-on test of 20 field medic tasks will be conducted before and after the military proficiency training. These tasks are: temperature, pulse, respiration, blood pressure, oropharyngeal airway, nasopharyngeal airway, supplemental oxygen administration, bag-valve-mask apneic patient with pulse, impalement injury, abdominal wound, chest wound, tourniquet, shock, splint-joint, splint-long bone, splint-traction, intravenous infusion, primary survey, mast survey, and secondary survey. Performance will be recorded as a Go or No Go on each task. Data averaged across n=60 field medics will be used as a comparative baseline for gauging the proficiency of IRR soldiers before and after a rapid train-up program of instruction designed for a mobilization.

Progress: This protocol has been terminated. It was never implemented.

DEPARTMENT OF NURSING

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): RN Lynn McNicol

PROTOCOL TITLE: Prospective Evaluation of Coccidioidomycosis in Human Immunodeficiency Virus-Infected Individuals Living in an Endemic Area

[redacted]

We conclude that 43% of our cohort was infected with Coccidioides as suggested by positive skin test. In follow up, 25% of the cohort had a CD 4 count<200, yet no one had developed coccidioidal infection.

DEPARTMENT OF NURSING

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): RN Lynn B. McNicol

PROTOCOL TITLE: A Review of HIV-Infected Women Evaluated at a Southwestern Military Medical Center

PROTOCOL #95/11 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): LTC Wellington Sun

Key Words: HIV, Women

Study Objective:

(1) Describe characteristics of HIV-infected women evaluated at William Beaumont Army Medicall Center. Characteristics of particular interest include duty status, marital status, race/ethnicity, source of referral for HIV testing, number of children, serostatus of spouse (if known), initial and most recent Walter Reed Stage and person months/years of follow-up within DoD.

(2) Assess the quantity and quality of data available for further study from existing files and the US Army HIV Data System.

Technical Approach: This is a descriptive retrospective case review study.

Progress: To dated 33 HIV infected women seen at WBAMC have been identified from Infectious Disease clinic files. Assessing the quantity and quality of data available from the US Army HIV Data Systems (USAHDS), which was one of the objectives of this study will not be possible. USAHDS as it was known when this study began no longer exists and as of MAR 97 can no longer be accessed without passwords and communications software provided to MTFs. The sole source for continued data collection for this study will be Infectious Disease clinic files.

DEPARTMENT OF NURSING

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): LTC Martha J. Skipper

PROTOCOL TITLE: Comparison Of Four Analgesic Agents For Venipuncture Pain

PROTOCOL #95/54 STATUS: Completed

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): CM Hackman, P Patterson, AA Hussa, KA Fedele, RL Gledhill, GL Vegh

Keywords: Venipuncture, Pain, Analgesic

Study Objective: The objectives of this study are : (1) to determine if a difference exists in the analgesic efficacy of the four analgesics, (2) to determine if there is a cost difference among these four analgesic groups, and (3) to determine if there is a convenience difference in the four groups. No studies were found in the literature comparing the four study analgesic agents in the above three areas simultaneously. This study will add empirical data for use by both Medicall clinicians as well as health care administrators.

Technical Approach: This study will be a completely randomized design. Subjects will be randomly assigned to treatment groups using a table of random numbers (Polit and Hungler, 1991). Subjects will be assigned to treatments in the order in which they volunteer for the study.
A sample of convenience will be utilized of patients who present for surgery over the time frame of the study. The subjects will be informed that they will receive an analgesic before the insertion of their 16 gauge IV catheter. They will not be made aware of any reported differences between the four types of analgesics, and to the extent possible, they will be unaware of the agent which they are receiving.

Progress: 248 subjects have been entered in the study with no adverse reactions reported to date.

ABSTRACT:
Introduction: Anesthesia administration requires intravenous access with large gauge catheters for the administration of fluids and medications. IV cannula insertion, or venipuncture, can be perceived as a painful and distressful event to an already anxious surgical patient. The rise of outpatient surgery has fostered the practice of unmedicated patients arriving to the operating room holding area with anticipatory fear of the surgical experience. Many of these patients have had prior encounters with venipuncture in other areas of the hospital which may have left painful memories due to the failure of the staff to obtund venipuncture pain with analgesics. Therefore, administration of an analgesic agent prior to catheter insertions is useful to prevent pain and optimize patient comfort and satisfaction. The qualities of the ideal analgesic agent are efficacy, patient acceptance, cost, and convenience of use by the anesthesia staff. This study seeks to address these multivarient factors in choosing an analgesic agent for venipuncture in today's health care system.
Methodology: After institutional review board approval, written consent was obtained from a convenience sample of 280 pre-operative patients. The study subjects were randomly assigned to one of four groups with each group receiving a different analgesic agent prior to venipuncture. Group I received 2.5% lidocaine - 2.5% prilocaine cream (LPC), Group II received dichlorotetra flouroethane spray (DCTF), Group III received 0.05% lidocaine

subcutaneously (lidocaine), and Group IV received normal saline with 0.9% benzyl alcohol subcutaneously (BA).

Pain of application was measured with the Verbal Descriptor Scale (VDS) and pain of cannulation was measured with the Visual Analog Scale (VAS). Cost was measured and compared on a unit dose basis. Convenience was measured with a questionnaire survey completed by the investigators.

Results: The data was analyzed using the General Linear Models Procedure of SAS 1991, Chi square, and Student's T test. There was a significant difference in pain of application among all four agents ($p<0.05$). There was a significant difference in cannulation pain between Groups I (LPC) and III (lidocaine ($p<0.05$) and between Groups II (DCTF) and III (lidocaine) ($p<0.05$). There was a significant difference in cost and convenience among the four agents.

Discussion: Benefits of this study to patients and staff were determining an effective, inexpensive, and convenient analgesic agent for venipuncture. Lidocaine and normal saline with 0.9% benzyl alcohol were shown to be effective, inexpensive, and convenient.

DEPARTMENT OF NURSING

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): LTC Anne Varner

PROTOCOL TITLE: Pediatric Intubation Training Utilizing the Ferret Model

PROTOCOL #88/65A STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): L Tremper

Key Words: Pediatric Advanced Life Support, pediatric intubation ferret

Study Objective: This training is designed to teach physicians and other health care professionals basic knowledge and endotracheal intubation skills required to resuscitate a neonate (newborn) or infant.

Technical Approach: The laboratory exercise described below will concentrate on developing the health professional's confidence in establishing an airway. Each new house officer will be required to intubate 2 ferrets employing a laryngoscope and endotracheal tube.

Animals will be anesthetized with ketamine HCL (22 mg/kg, given intramuscularly), with atropine (0.04 mg/kg, subcutaneously). Up to 2 additional half-doses (11 mg/kg) of ketamine may be given if needed. Pre-anesthesia with tranquilizer (Acepromazine, 0.2 mg/kg, subcutaneously) may be given to allow easier intubation for first-time trainees. Administration and monitoring of anesthesia will be directly supervised or performed by the attending veterinarian. The veterinarian will be present at all times to assist, modify, or terminate the procedure. Butorphanol tartrate (0.2 mg/kg SC every 8 hours) will be administered after the procedure to alleviate any possible pain.

At the discretion of the instructor, the stages and planes of anesthesia may be defined and assessed by the students. The animal will be placed in dorsal recumbency. Each trainee will visualize the larynx, noting the similarity of the feline larynx to that of the human infant; palpate larynx externally; and perform visual intubation using the laryngoscope and endotracheal tube.

Two animals will be intubated by each first-time trainee in each laboratory session. Previously trained individuals will use one animal.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).
Amendment Jun 93: Feline model changed to ferret model. Principal investigator is MAJ Varner.

Progress: 140 Nursing students have been enrolled in this study. Ferrets are used to train nursing and medical staff on pediatric intubation.

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): LTC Wanda A. Morgan

PROTOCOL TITLE: Dietary Sources of Omega-3 Fatty Acids in Subjects with Hyperlipidemia

PROTOCOL #96/03 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): VR Zilling

Key Words:

Study Objective To quantify the amount of omega-3 fatty acids in the diets of individuals who are receiving nutrition counseling for hyperlipidemia.

Study Design: Prospective descriptional study.

Progress: No progress was reported by PI. LTC Morgan is a reservist.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Ruben Alvero

PROTOCOL TITLE: Vasoactive Intestinal Peptide in Early Human Pregnancy

PROTOCOL #96/01 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

Key Words: Vasoactive intestinal peptide, embryonic development

Study Objective: Current animal studies have definitively shown that VIP is critical to normal embryonic development during a critical window that corresponds to post-conception days 26-30 in the human. Currently no literature exists to describe early human pregnancy VIP dynamics. The purpose of this study is describe for the first time plasma levels of VIP within 6 weeks of conception.

Study design: Prospective collection of maternal plasma samples in the first six weeks of pregnancy with characterization of a VIP concentration curve in early gestation. Serial ultrasonography in these patients to confirm normal gestation.

Progress: 27 subjects have been entered in this study with no adverse reactions reported to date.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: GOG #90, Evaluation of Cisplatin, Etoposide and Bleomycin (BEP) Induction followed by Vincristine, Dactinomycin and Cyclophoshamide (VAC) Consolidation in Advanced Ovarian Germ Cell
Tumors

PROTOCOL #91/67 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Hawley-Bowland

Key Words: Ovarian Germ Cell Cancer

Study Objective: To evaluate the effect of induction chemotherapy with cisplatin plus etoposide plus bleomycin (BEP) followed by consolidation with vincristine plus dactinomycin plus cyclophoshamide (VAC) in previously untreated patients with advanced ovarian germ cell tumors. To evaluate the effect of BEP chemotherapy in patients with recurrent or progressive disease during or after previous non-cisplatin containing chemotherapy. To further investigate the relevant prognostic factors. To evaluate the acute and chronic toxicity of such chemotherapy. particularly in gonadal and reproductive function. To evaluate the effect of chemotherapy on menstrual status and reproductive function in patients in whom the uterus and one tube and ovary are preserved.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Closed by GOG.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: GOG #93, Evaluation of intraperitoneal chromic phosphate suspension therapy following negative second-look laparotomy for Epithelial Ovarian Carcinoma

PROTOCOL #91/68 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Hawley-Bowland

Key Words: Ovarian Epithelial Cancer

Study Objective: To evaluate the efficacy of P32 therapy in patients with no residual ovarian cancer and to evaluate the morbidity from intraperitoneal P32 therapy.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: No patients have been enrolled to date.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: GOG #122, Whole Abdominal Radiotherapy versus Circadian-Timed Combination Doxorubicin-Cisplatin Chemotherapy in Advanced Endometrial Carcinoma

PROTOCOL #92/30 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Hawley-Bowland

Key Words: Endometrial Carcinoma (Advanced)

Study Objective: To compare treatment outcomes (survival and progression free interval) and failure patterns in patients with stages III and IV endometrial carcinoma (< 2cm residual disease) treated with whole abdominal irradiation versus circadian-timed combination doxorubicin-cisplatin chemotherapy. To determine and compare the incidence and type of acute and late adverse events observed with the two treatment regimens.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: No patients have been enrolled to date.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: GOG #109, A Randomized Comparison of 5-Fu Infusion and Bolus Cisplatin as an Adjunct to Radiation Therapy versus Radiation Therapy Alone in Selected Patients with Stages IA2, IB and IIA Carcinoma of the Cervix Following Radical Hysterectomy and Node Dissection

PROTOCOL #92/34 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Hawley-Bowland

Key Words: Cervical Carcinoma

Study Objective: To determine whether the combination of 5-fluorouracil (%-FU) and cisplatin used as an adjunct to radiation therapy will improve survival rate or progression-free survival and decrease extra pelvic failure compared to radiation therapy alone in patients with positive pelvic lymph nodes, positive parametrial involvement or positive surgical margins following radical hysterectomy and lymph node dissection for stages IA2, IB, and IIA carcinoma of the cervix. To determine the increase in toxicities due to 5-FU and cisplatin as an adjunct to radiation therapy versus radiation therapy alone.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: No patients enrolled to date.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: GOG #114, Phase III Randomized Study of IV Cisplatin and Cyclophosphamide vs IV Cisplatin and Taxol Vs High Dose IV Carboplatin followed by IV Taxol and Intraperitoneal Cisplatin in Patients with Optimal Stage III Epithelial Ovarian Carcinoma

PROTOCOL #92/51 STATUS: Open

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): OB/GYN Staff

Key Works: Epithelial Ovarian Carcinoma

Study Objective: To compare recurrence-free interval, complete pathologic response, and survival between the standard regimen of intravenous cisplatin/cyclophosphamide and the two experimental regimens: (1) intravenous cisplatin/taxol and (2) intraperitoneal carboplatin

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: GOG #135, Evaluation of Drug Sensitivity and Resistance with the ATP-Cell Viability Assay (ATP-CVA)

PROTOCOL #92/52 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): OB/GYN Staff

Key Words: ATP-CVA, ATP, Cell Viability

Study Objective: To evaluate the correlation between the ATP-cell assay and patient response to chemotherapy in untreated primary epithelial ovarian carcinoma; to correlate laboratory results with the achievement of pathologic CR at time of second look surgery; to correlate laboratory results with progression-free survival; and to correlate single agent and combined agents in vitro studies with clinical outcome. Single drugs as well as drug combinations will be tested in vitro.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: One patient was enrolled in this study with no adverse reactions reported to date. This protocol has been closed by the GOG.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: GOG #134/NCCTG #92-61-51, A Phase III Trial of Taxol at Three Dose Levels and C-CSF at Two Dose Levels in Platinum-Resistant Ovarian Carcinoma

PROTOCOL #92/63 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

Key Words: Ovarian Carcinoma

Study Objective: To determine if the dose of Taxol affects response rate, progression free interval or survival in patients with platinum-resistant ovarian cancer; to compare the toxicities of the three regimens; to compare the efficacy and toxicity of two dose levels of G-CSF (5 micrograms/kg/day versus 10 micrograms/kg/day) in patients who receive the highest Taxol dose (250 mg/m^2); and to determine the relationship between peak Taxol plasma concentration and toxicity/response.

Technical Approach: Details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: No patients have been enrolled to date. This protocol has been closed by GOG.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: GOG #136, Acquisition of Human Ovarian and Other Tissue Specimens and Serum to be Used in Studying Causes, Diagnosis, Prevention and Treatment of Ovarian Cancer

PROTOCOL #93/14 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

Key Words: Ovarian Carcinoma, Tumor Bank

Study Objective: To accomplish the collection of human ovarian tissue specimens and serum within GOG participating institutions; to provide a repository for long term storage of ovarian tumor, tissue, and serum. This material will be used in studies to better understand the molecular biology of ovarian tumors; and to make available. through the Cooperative Human Tissue Network (CHTN), tumor tissue and serum for proposed projects conducted by GOG Investigators (internal bank) and by researchers nationally (external bank).

Technical Approach: Details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: 19 patients have been enrolled with no adverse reactions.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: GOG #140, An Assessment of Age and Other Factors Influencing Protocol versus Alternative Treatments for Patients with Epithelial Ovarian Cancer Referred to Gynecologic Oncology Group Institutions

PROTOCOL #93/21 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

Key Words: Epithelial Ovarian Cancer

Study Objective: To assess the frequency at which patients with epithelial ovarian cancer are enrolled in prospective clinical studies at institutions participating in gynecologic oncology group protocols; to assess whether patient age affects enrollment in prospective gynecologic oncology group protocols; and to assess what demographic or clinicopathologic factors affect patient enrollment in prospective gynecologic oncology group protocols.

Technical Approach: Details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: No patients enrolled to date. This protocol was closed by GOG.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: GOG # 9207, Laparoscopic retroperitoneal lymph node sampling followed by immediate laparotomy in women with cancers of the cervix

PROTOCOL #93/42 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

Key Words: Laparoscopic, Cancer of Cervix

Study Objective: To determine the adequacy of laparoscopic sampling of pelvic and aortic lymph nodes by immediate laparotomy in women with cancers of the cervix.

To obtain information of adverse effects and difficulties associated with laparoscopic sampling of pelvic and aortic lymph nodes.

Technical Approach: Details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: No patients have been enrolled to date. This protocol has been closed by GOG.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: GOG # 144, Molecular genetic analysis of ovarian cancer families

PROTOCOL #93/48 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

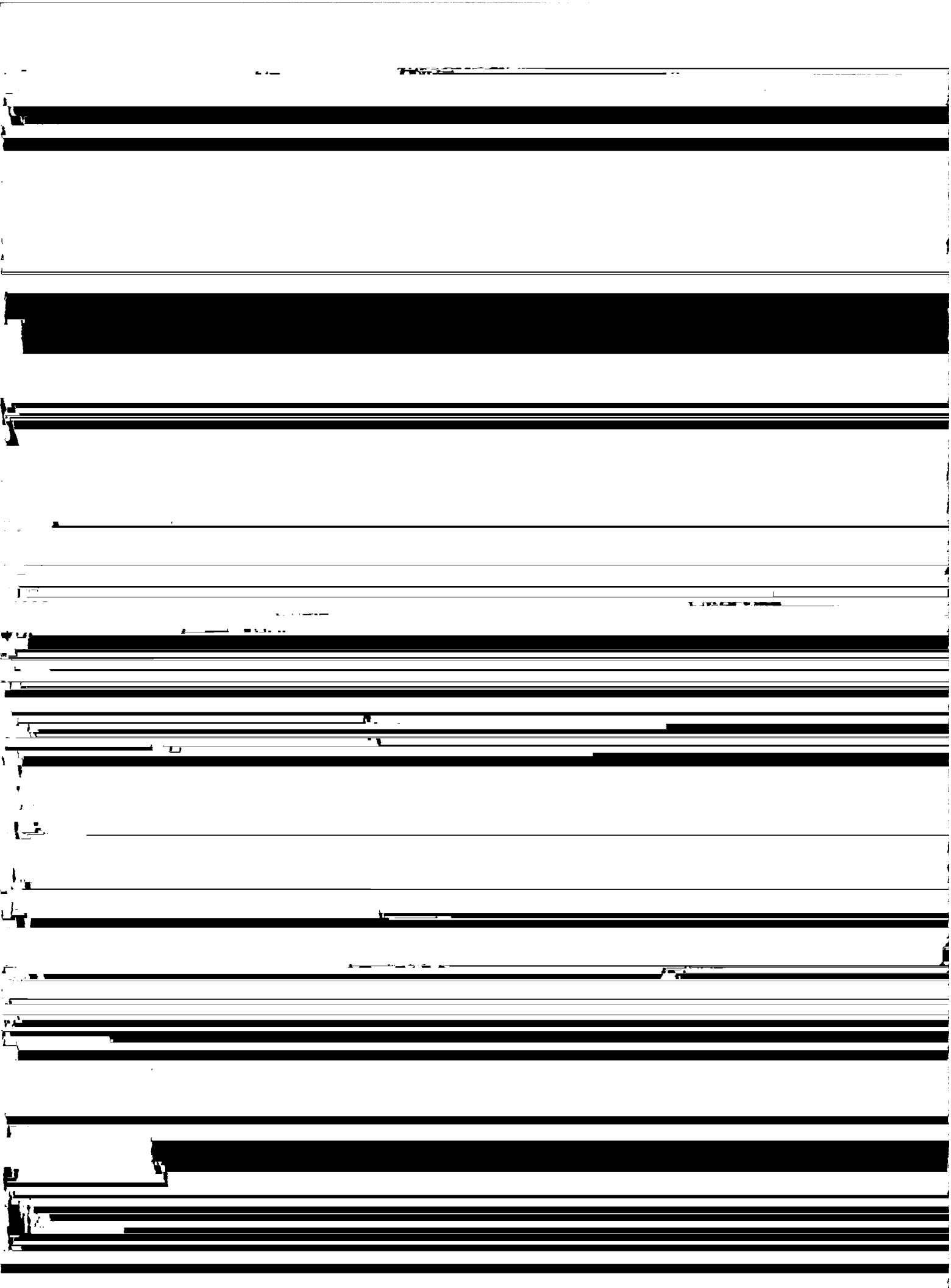
Key Words: Genetic Analysis, Ovarian Cancer Families

Study Objective:

1. To determine the frequency of chromosomal rearrangements in women with familial ovarian cancer.
2. To identify genetic markers linked to familial ovarian cancer.
3. To identify deletions or rearrangements that signal the site of the mutation.

Technical Approach: Details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: No patients enrolled to date.



DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: Protocol GOG #151, A Phase II Trial of Intraperitoneal Paclitaxel (Taxol) as Salvage Therapy in Patients with Small Volume Residual Ovarian Cancer Following Initial Systemic Chemotherapy

PROTOCOL #95/34 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): None

Keywords: Ovarian Cancer

Study Objective: To determine the surgically defined objective response rate of intraperitoneal Paclitaxel (Taxol) when administered on a weekly schedule to patients with small volume residual ovarian cancer following initial systemic chemotherapy.

To further evaluate the safety of intraperitoneal Paclitaxel administered on a weekly schedule as a salvage treatment program to patients with ovarian cancer.

Technical Approach: All subjects must have a reassessment laparotomy per GOG surgical manual for disease measurement prior to therapy on this study. At completion of treatment, subjects may initially undergo laparotomy to verify response, but a laparotomy must be performed if no disease is detected at laparoscopy.

The drug or drugs will be administered intraperitoneally through an implantable peritoneal dialysis catheter i.e., Tenckhoff center, which may be connected to an indwelling port, such as a Port-A-Cath. The catheter will be placed at the time of second-look laparotomy or at a subsequent operation. Surgical placement of catheters should be performed according to GOG guidelines. These catheters are inserted into the peritoneal cavity, tunneled through the subcutaneous tissue, and either exteriorized through a stab incision (Tenckhoff catheter), or the implantable port, i.e., Port-A-Cath, is placed in the subcutaneous tissue of the anterior, inferior thorax.

Progress: No patients have been enrolled in this study to date. This protocol has been closed by GOG.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: Protocol GOG #154, Human Immunodeficiency Virus Testing In Patients with Invasive Cervical Carcinoma

PROTOCOL #95/35 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): NA

Keywords: HIV, Cervical Carcinoma

Study Objective:

To determine the frequency of HIV serostatus among patients 50 or under who present with invasive cervical cancer and who consent to HIV testing.

To correlate HIV serostatus with various clinical, pathologic, epidemiologic and demographic factors.

To obtain preliminary data comparing the clinical course, response to therapy and toxicity of therapeutic regimens for HIV-positive women to those for HIV-negative women with similar disease status.

Technical Approach:

HIV Testing - Part A

Patients will be tested for HIV. Either one of both the ELISA or Western Blot tests will be administered. Confirmation of HIV serostatus - results of HIV testing (4 copies) must be submitted along with HIV test result form.

For HIV negative result: Negative ELISA test (or appropriate substitute test must be FDA approved).

For HIV positive result: Positive ELISA plus positive Western Blot (or appropriate substitute must be FDA approved).

Pathology: Confirmation of diagnosis of invasive cervical cancer.

Progress: 1 patient has been enrolled in this study with no adverse reactions to date.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: GOG #150, A Phase III Randomized Study of Accelerated Hyperfractionated Whole Abdominal Radiotherapy (AHWAR) Versus Combination Ifosfamide-Mesna with Cisplatin in Optimally Debulked Stage I, II, III, or IV Carcinosarcoma (CS) of the Uterus

PROTOCOL #95/47 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): None

Keywords:

Study Objective: To compare treatment outcomes (survival and progresso-free interval) and failure patterns in patients it stgs I-IV carcinosarcoma (CS) of the uterus ($\leq$ 1 cm residual disese) without extra-abdominal distant disease treated with AHWAR versus cisplatin and ifosfamide/mesna.

To determine and compare the incidence and type of acute and late adverse events observed with the two treatment regimens.

Technical Approach: Details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: No patients have been enrolled in this study to date.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: The Evaluation of the Intrinsic Tensile Strength of Rectus Fascia Incised with a Scalpel versus the Electrosurgical Instrument

PROTOCOL #95/50A STATUS: Completed

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): None

Keywords:

Study Objective: To evaluate the intrinsic tensile strength of rectus fascia incised with a scalpel versus the electrosurgical instrument.

Technical Approach: The electrosurgical instrument is used daily in operating suites throughout the world. The surgeon's use of this instrument is frequently based on their exposure during their training and not based on objective data. Consequently, the electrosurgical instrument has frequently been used to incise the rectus abdominis fascia while performing a laparotomy without any understanding of the healing implications of doing so. In general, there is a paucity of data concerning the healing ability of tissues after conducting an electrical current. The only comparison data of wound healing to date is the observance of macrophages and neutrophils in the histologic specimen of wounds created by a scalpel verses the electrosurgical instrument. The infiltration of these inflammatory cells appeared to be directly related to the power setting of the instrument and the speed at which it traveled.

Progress: Study completed, abstract presented at ACOG AFD on 10/21/96 - was the ACOG Chairman's Award for best clinical paper. Several follow-up protocols are being submitted.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: GOG #157, Randomized Phase III Trial of Carboplatin (AUC 7.5) and Paclitaxel 175 MG/M^2 Q 21 Days X 3 Courses Versus the same Regimen X 6 Courses, in Patients with Selected Stage IC and II (A, B, C) and Selected Stage IA and IB Ovarian Cancer

PROTOCOL #95/51 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): None

Keywords: Tumor, Pelvic Extension, Malignant Ascites, Peritoneal Washings

Study Objective: In definitively staged patients who have tumor involving one or both ovaries with pelvic extension (completely resected) and/or malignant ascites and/or positive peritoneal washings (Stages I-C, II-A, II-B, II-C with no macroscopic residual disease), and in those Stage I-A and I-B patients with poorly differentiated tumors.

(1)_ To compare the progression-free interval and overall survival of the two treatment regimens.

(2) To define the relative toxicities of the two treatment approaches.

Technical Approach: Details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress No patients have been enrolled in this study to date.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: GOG # 152, A Phase III Randomized Study of Cisplatin (NSC#119875) and Taxol (Paclitaxel) (NSC #12973) with Interval Secondary Cytoreduction vs. Cisplatin and Paclitaxel in Patients with Suboptimal Stage III, & Selected Stage IV Epithelial Ovarian Carcinoma

PROTOCOL #95/52 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): None

Key Words: Epithelial Ovarian Carcinoma

Study Objective: To determine if secondary cytoreductive surgery contributes favorably to progression-free interval and survival in patients with suboptimally debulked stage III & selected stage IV epithelial ovarian cancer.

To determine the morbidity of secondary cytoreducive surgery in patients with suboptimally debulked stage III & selected stage IV epithelial ovarian cancer.

To prospectively assess the quality of life of suboptimally debulked stage III & selected stage IV epithelial ovarian cancer patients and to determine if secondary cytoredutive surgery affects their quality of life.

Technical Approach: Details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: No patients have been entered in this study to date.

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DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: GOG #158, A Phase III Randomized Study of Cisplatin and Paclitaxel (24-Hour Infusion) versus Carboplatin and Paclitaxel (3-Hour Infusion) in Optimal Stage III Epithelial Ovarian Carcinoma

PROTOCOL #96/02 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): None

Key Words:

Study Objective: This study will compare recurrence-free interval, and survival in patients with optimal ($\leq$ 1 cm residual) stage III epithelial ovarian cancer who are either receiving Cisplatin and Paclitaxel or Carboplatin and Paclitaxel (See GOG Protocol page 1). This is a multi-center study coordinated by the Gynecologic Oncology Group. WBAMC's role in the study will include patient recruitment, patient treatment, data collection, and submission of data to GOG for analysis.

Technical Approach: Randomized phase III clinical trial.

Progress: No patients have been enrolled to date in this study.

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DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: Protocol GOG #148, The Clinical Utility of Soluble TNF/LT Membrane Receptors in the Serum of Patients with all Stages of Primary Epithelial Ovarian Cancer

PROTOCOL #96/09 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): None

Key Words:

Study Objective: This study will characterize serum concentrations of soluble tumor necrosis factor (NTF) and lymphotoxin receptors, as related to cancer stage and treatment, in patients with primary epithelial ovarian cancer (See GOG Protocol page 1). This is a multi-center study coordinated by the Gynecologic Oncology Group. WBAMC's role in the study will include patient recruitment, patient treatment, data collection, and submission of data to the GOG for analysis.

[redacted]

Progress: No patients have been enrolled to date in this study.

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DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Jay W. Carlson

PROTOCOL TITLE: GOG Protocol # 162 A Phase III Randomized Trial of Cisplatin (NSC #119875) With Paclitaxel (NSC #125973) Administered by Either 24 Hour Infusion or 96 Hour Infusion in Patients With Selected Stage III and Stage IV Epithelial Ovarian Cancer

PROTOCOL #96/17 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): OB/GYN Staff

Keywords:

Study Objective:

1. To compare progression-free survival, overall survival and frequency of response of 24-hour versus 96-hour paclitaxel (Taxol) infusions, each combined with cisplatin, in the treatment of selected stage III and stage IV epithelial ovarian cancer.

2. To determine the incidence and severity of adverse events, including catheter complications and chemotherapy toxicity, for 96-hour infusions of paclitaxel.

3. To examine the relationships between plasma paclitaxel concentrations and measures of drug toxicity and response in both 24-hour and 96-hour infusion schedules.

Technical Approach: Patients will be registered to this study by telephone and eligibility will be verified by the fast-fact verification procedure. At the time of registration the participating institution will be identified and whether or not the patient has clinically measurable disease will be determined. The patient will be stratified based on these two factors and the treatment assignments will be randomized with equal probability within blocks in each stratum.

Progress: No patients have been enrolled to date in this study.

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DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): CPT Barry Green

PROTOCOL TITLE: Incidence and Physiologic Spectrum of Visual Changes in Subjects Taking Clomiphene Citrate

PROTOCOL #96/29 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): K Koski, R Alvero, J Behan

Key Words:

Study Objective: To determine the incidence and spectrum of visual changes in patients taking Clomiphene to induce ovulation.

Study design: Prospective observational study.

Progress: Protocol is in progress but no subjects have been identified to date. Estimated completin date has been changed to Sep 97.

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DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): CPT Kristine A. Eule

PROTOCOL TITLE: Modified Cytobrush Technique Versus Endocervical Curettage In The Evaluation Of Cervical Dysplasia

PROTOCOL #95/22 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): J Szigeti, R Gomez

Keywords: Modified Cytobrush, Endovervical Currettage

Study Objective: To show that a sleeved cytobrush technique is a better method of endocervical evaluation than the currently practiced ECC.

Technical Approach: Prospective data collection. All patients referred to the dysplasia clinic who meet inclusion criteria will receive the usual evaluation including colposcopy, repeat PAP, ECC, and cervical biopsies as indicated. Instead of the standard cytobrush a sleeved cytobrush will be used to do the PAP. The glass slide for the PAP will be divided in two by etching with a diamond pencil, and the cytobrush endocervical specimen will be rolled out on one half and the ectocervical spatula specimen placed on the other half. The slide will be processed in the usual manner for cytology. The pathology report will comment on which parts of the slide any abnormality / pathology is found. The ECC will be processed and read as usual. Patients with dyplasia or findings worrisome for cancer on either ECC or endocervical cytobrush cytology will then undergo CKC - this is the actual study group. The CKC findings shall be considered the "gold standard" for assessing endocervical pathology. Each study case will have all pathology reviewed by Dr. Richard Gomez, Department of Pathology co-investigator. The sensitivity, specificity, and positive and negative predictive values will then be determined for ECC versus sleeved cytobrush cytology to determine if a statitically significant ($p<0.05$) difference exists. Statistical analysis will be performed under the guidance of Lyle Broemeling, our statistical consultant.

Progress: 60 subjects have been entered in the study with no adverse reactions noted to date. The estimated completion date has changed from Nov 96 to Mar 97. Out of the large number of patients seen in the Dysplasia Clinic, only a very few ultimately undergo a LEEP or a cone biopsy (~ 1/100 patients). Originally, we had anticipated a larger number of such patients. Currently, we can not even make preliminary conclusions on our limited data. Nevertheless, we anticipate that we will be able to obtain sufficient numbers within a reasonable time period.

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[redacted]

women, assess attitudes about medical care for mastodynia and either support or refute a role for progesterones in the prevention and treatment of this common condition.

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[redacted]

PROTOCOL TITLE: Effect on Psyllium Fiber on Serum Glucose Levels after Abnormal 3 hour 100 gram Oral Glucola Tolerance Test in Pregnant Patients

PROTOCOL #95/10

STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): JW Carlson

Keywords: Glucola Test, Pregnant Patients

Purpose: To determine if dietary fiber supplementation (with commercially available flavored psyllium wafers) influences serum glucose levels in pregnant patients with a previously documented abnormal 1 hour 50 gram glucola test.

Technical Approach: Two groups of obstetric patients will be enrolled. All patients will undergo the standard diabetes screening at 24-28 weeks EGA, consisting of a 50 gram glucola challenge with serum glucose determination 1 hour later. Patients with abnormal values will be offered participation in the study. Each group will consist of 50 randomly assigned patients. One group will supplement their pre-existing diets with Metamucil wafers (2 wafers QID) for 72 hours. All patients will repeat the 50 gram glucola challenge 4 days after the initial screening test. Each patient will serve as her own control.
Amendment #1: Submitted 27 Mar 95. Current FDA approval of Metamucil dosing TID, the protocol will change to dietary fiber supplementation TID with meals. (Previously: QID, with meals and HS).
Protocol will also change to use of the sugar-free powder product which contains only 2 cal/dose. (Previously: fiber wafers containing 100 cal/dose).
Amendment #2: Submitted 10 Oct 95. Change from 1 hour to 3 hours and 50 grams of Glucola to 100 grams. This protocol was made into a multi-center military study.

Progress: This protocol was intended to be a multi-center military study. Grant money had been received. This protocol was terminated, however, due to lack of participation by other institutions in the face of relatively low diabetic population at WBAMC. This study could not be completed in a timely fashion by enrolling only WBAMC population. All CRDA money received was returned to Procter and Gamble Corp.

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DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): CPT Natalie J. Hoshaw

PROTOCOL TITLE: The Role of Three Phase Bone Scintigraphy in Women with Lower Back, Pelvic or Hip Pain

PROTOCOL #95/44 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): AJ Moreno, JW Carlson

Keywords: Chronic Pelvic Pain, (3 Phase) Bone Scintigraphy

Study Objective: The objective of this study is to perform a bone scan over the anterior pelvis with blood flow and blood pool views in women being evaluated in the gynecology clinic for lower back, pelvic or hip pain. The bone scan images will be reviewed for the occurrence, size, location, and uptake characteristics of the pelvic pathology. Other imaging methods, such as ultrasonography, computer tomography (CT), or magnetic resonance imaging (MRI) will be done to further characterize the pelvic pathology.

Technical Approach: The subjects selected for this study will be from patients being evaluated in the gynecology clinic for lower back, pelvic or hip pain. A bone scan will be performed on the patients selected for participation in this study. The bone scan will include blood flow and immediate blood pool images of the anterior pelvis. The findings on the scan will then be correlated with the gynecologic workup, to include pelvic examination, possible ultrasonography, CT or MRI, and possible laparoscopy/laparotomy. The bone scan findings will be correlated to the pelvic pathology in terms of size, type, and location. The incidence of soft-tissue pelvic pathology in women undergoing evaluation for lower back, pelvic or hip pain will be determined.

Progress: To date 23 patients enrolled in the pain arm of the study (anticipated 35) and 2 control patients. Patients with pelvic or low back pain are reasonably willing to undergo the study, however, control patients have been scarce. It is more difficult to find "asymptomatic" (except for symptoms of uterine prolapse) to receive IV radiopharmaceutical. So far, two for two controls have had positive bone scans but negative pathology. If we get 5-10 more controls with the same, I think we will be able to close/finish the study. At this time, we will need another 6-12 months to enroll ~ 12 more pain patients as well as the above mentioned controls.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): CPT G. Larry Maxwell

PROTOCOL TITLE: Perinatal Transmission Rates of Human Papilloma Virus in Various Maternal Fluids

PROTOCOL #94/25 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): M Zacharean, JW Carlson, AP Soisson, WF Nauschuetz, F Harlass

Key Words: HPV, Prenatal Transplacental Transmission

Study Objective: The purpose of this prospective blinded trial is two-fold:

1. To determine the incidence & respective viral DNA type of HPV in cervical & peripheral blood specimens of pregnant patients.

2. To determine the perinatal transmission rate of HPV by perinatal analysis of transabdominally collected amniotic fluid as well as maternal/fetal blood and breast milk taken immediately postpartum.

Technical Approach: A total of 100 patients will be entered in this prospective study. It is a collaborative study between WBAMC and Texas Tech. Each patient will have cervical swab & amniotic fluid samples analyzed for HPV type using PCR amplification techniques. Maternal and cord blood samples and breast milk samples will be analyzed on those patients identified as HPV positive; similar techniques will be used in determining the presence and type of HPV. Questionnaires will also be filled out on each participant in order to provide demographic data for statistical comparison (i.e., age, gravidy, paridy, smoking history, race, sexual history, past medical problems, history of abnormal PAP smears, indication for amniocentesis, gestational age).

Amendment #1 (Apr 94): Changed title from "Determination of Prenatal Transplacental Transmission Rates of HPV in an Infected Pregnant Population" to present title. Added breast milk as sample to be obtained. Added M Zacharean as an associate investigator.

Amendment #2 (May 94): Funding implications modified.

Progress: This study was initially opened by Dr. Maxwell (1994). I assumed data collection after his graduation/departure. HPV isolations techniques were plagued with errors and all samples were discarded. Given this study would have to start from ground zero, I offered the protocol to my OB/GYN colleagues. The protocol was closed due to lack of interest. A new but similar protocol is being developed by Drs. Brill, Williams and myself and will be submitted to a future IRB for approval.

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DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): CPT Roger J. Rembecki

PROTOCOL TITLE: Platelet Count Changes in Term, Low Risk Deliveries

PROTOCOL #94/29 STATUS: Completed

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): P Bayliss

Study Objective: Determine platelet count changes in term, low risk deliveries.

Technical Approach: We will review the platelet counts measured at parturition and post partum (less than or equal to 48 hours). Data will be analyzed to discover significant changes chronologically and significant differences between vaginal and cesarean deliveries.

Progress: Abstract was presented at the Armed Forces District meeting, November 1995.

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DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Julius Szigeti

PROTOCOL TITLE: OB/GYN Bowel Training Utilizing the Pig Model

PROTOCOL #86/08A STATUS: Inactive

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

Surgical Training in Residency - GI

Study Objective: This training is designed to teach physicians the basic knowledge and operative skills required to perform basic small and large bowel surgery.

Technical Approach: The laboratory exercise described will concentrate on developing the surgeons confidence in recognizing bowel injuries, resecting and anastomosing small bowel, and large bowel exteriorization. To accomplish these training objectives, one survival and one non-survival surgical training procedure will be conducted on each animal assigned to the protocol. The first surgery consists of small bowel resection and re-anastomosis. The surgical site is then closed and the animal awakens from anesthesia. The surgical procedure and post operative care will be conducted as stated below. After approximately three weeks, a second laparotomy will be conducted and the training will consist of resecting the colon and creating a colostomy. Afterward, the surgical site will be closed and euthanasia administered while the animal is still anesthetized.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: This protocol is currently inactive. No animals were used last year (96). This protocol will be presented again before activating.

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DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Julius Szigeti

PROTOCOL TITLE: Genitourinary Tract Surgery Training Utilizing a Pig Model and Comparing Stenting Technique

PROTOCOL #86/64A STATUS: Inactive

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): LTC Harris

Key Words: Surgery Training, Genitourinary Tract

Study Objective: This training is designed to teach resident physicians the basic knowledge and operative skills required to perform genitourinary surgery while simultaneously evaluating the need for ureteral stenting following the operative procedures.

Technical Approach: The laboratory exercise described will concentrate on developing the surgeons confidence in recognizing GU injuries, resecting and anastomosing ureters, and reimplanting ureters into the urinary bladder. To accomplish these training objectives, one survival and one non-survival surgical training procedure will be conducted on each animal assigned to the protocol. The first surgery will consists of unilateral ureter resection and re-anastomosis. Upon completion of this procedure, the laparotomy incision will be closed and the animal awakens from anesthesia. The surgical procedure and post operative care will be conducted as stated below. After approximately three weeks, a second laparotomy will be conducted and the training will consist of transecting the contralateral ureter at the point of entry into the urinary bladder and reimplanting the ureter through the bladder wall. Afterward, the laparotomy incision will be closed and euthanasia administer while the animal is still anesthetized.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: This protocol is currently inactive. Future status is unknown.

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DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): CPT Nathan Tillotson

PROTOCOL TITLE: The Role Of The Inflammatory Pap Smear In Preterm Delivery

PROTOCOL #95/24 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Butterfield, S Borquaye, JS Bembry

Keywords: Pregnancy, Pap Smear, Inflammatory, Preterm

Study Objective: Determine if the inflammatory pap smear correlates with preterm delivery and if treating patients with inflammatory pap smears during pregnancy decreases the preterm delivery rate.

Study Design: Retrospective.

Progess: This study has been terminated by MAJ Jay W. Carlson, Chief, OB/GYN, due to PCS of principal investigator.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Alvero, Ruben J. VanWeelden, Linda J.

PROTOCOL TITLE: The Effects of Medroxyprogesterone Acetate for Contraception on Bone Mineral Density

PROTOCOL #96/14 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): J Enriquez, SN Bhattacharyya, AJ Moreno,

Keywords: Depo-Provera, Bone mineral density

Study Objective: Based upon concerns stated in the introduction, the objectives of this study are as follows:

1. To determine the effects of DMPA use on bone mineral density in women. The first study group will consist of DMPA users. The second study group will be DMPA users with hormone replacement therapy. The control group will be an age-matched cohort of women not using DMPA or other types of hormone therapy.
2. To determine the prevalence and types of side effects in the DMPA user.
3. To correlate serum E_2 levels and urine bone metabolism values and bone
4. mineral density in the DMPA user.
5. To provide recommendations regarding the need of hormone replacement therapy in the DMPA user.
6. To provide recommendations regarding the counseling and patient education of women desiring to use DMPA for contraception.

Study design: This prospective study will examine females in the OB/GYN family planning clinic at William Beaumont Army Medical Center (WBAMC), El Paso, TX. Volunteers will be found primarily among women desiring to start DMPA for the first time.

Subjects must be between the ages of 20-35, non-pregnant and free from incurrent disease. The study will involve active duty women who meet height and weight and who have passed an APFT within the last 6 months. Subjects must be eumenorrheic (menstrual interval < 35 days). Women who smoke will be excluded from this study. Volunteers will be eligible if they have not smoked in the past year. Women who have taken DMPA or are on any type of hormone therapy will be excluded. Demographic data including age and race will be collected.

Forty-four subjects will be recruited and randomly assigned to two groups of 22 women. The protocol will be explained and a consent form must be signed. One study group will be given DMPA in the standard 90 day intervals. The second study group will also be given DMPA in the standard 90 day intervals. In addition, these women will be given hormone add-back therapy in the form of an Estraderm-TTS patches (50 ug), changed twice weekly

hydroxypyridinoline levels obtained. At the 6 month visit, a DEXA scan will be done in addition to serum E_2 and urinary testing of NTx, and deoxypyridinoline to conclude the study.

Progress: No subjects have been entered in this study.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): CPT Allen Walker

PROTOCOL TITLE: Ligature Tension of Laparoscopic Knot Tying: A Comparison of Various Methods

PROTOCOL #96/23 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): J Szigeti, JW Carlson, R Zabenko

Keywords: laparoscopy, ligature, tension

Study Objective: To compare the ligature tension applied with various methods of laparoscopic suture techniques.

Study design: This will be a 3x5 factorial design with two replications. Two surgeons will each perform one replication. There are three knots and five suture materials to be tested. Each surgeon will tie 15 of each knot using each suture, for a total of 75 of each type of knot. Over the two replications, 150 of each type of knot will be tied. All suturing will be performed in a pelvic trainer and will take place at Texas Tech University Health Sciences Center. We will study three types of laparoscopic knots: Roeder, the extracorpeal sliding square knot, and the Endoloop. Suture materials studied will be Ethibond, Prolene, Vicryl, Monocryl, and chromic gut. We will use 0-gauge suture. There will be 15 of each knot type tied with each type of suture.

All knots will be tied on a jig made of two hex-head screws and fastened to a tensiometer. The laparoscopic knots will be tied on the jig while fixed in a device for laparoscopic pelvic surgical training. A Ranfac knot pusher will be used in tying the Roeder knot and extracorpeal square note. Because surgeon fatigue can be a factor, all knots will be tied in random order based on a computer-generated table of random numbers. To increase external validity, the surgeons will wear latex surgical gloves while tying knots. The pelvic trainer will also have a dark, tinted covering to prevent the operators from directly viewing the knots as they are applied. A laparoscopic camera and monitor will be used to visualize placement on the jigs.

A tensiometer will be used to measure ligature tension applied. The tensiometer operator will be blinded to the type of suture being used, the operator, and the type of knot.

Progress: The following poster sessions and presentations have been conducted on this protocol. 34th American College of Obstetrics and Gynecologic Armed Forces District, San Diego, CA, 2-5 Oct 95; 35th American College of Obstetrics and Gynecologic Armed Forces District, Nashville, TN, 20-24 Oct 96. The estimated completion date has been extended to Feb 97.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): CPT Gary C. Wharton

PROTOCOL TITLE: Evaluation of Phenobarbital in the Prevention of Intraventricular Hemorrhage in the Very Low Birth Weight Infant (<1500gms or 32 Weeks)

PROTOCOL #91/28 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): FE Harlass

Key Words: Intraventricular Hemorrhage, Phenobarbital

Study Objective: To retrospectively compare WBAMC records where the current standard of care includes phenobarbital administration to any mother suspected or imminently delivering an infant 15gms or less, to those of R. E. Thomason General Hospital (RETGH), where the current standard of care does not include this administration. Through this comparison, an attempt will be made to demonstrate that such administration is beneficial in reducing the incidence and severity of intraventricular hemorrhage in this population as previously suggested.

Technical Approach: This will be a retrospective case controlled analysis of maternal and infant records. WBAMC's experience will be controlled with the experience at RETGH.

Progress: This study is terminated due to principal investigator leaving WBAMC. It has not been supported by new perinatologist or the literature after large study was recently published.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Michael Wood

PROTOCOL TITLE: Sterilization Regret in a Military Population

PROTOCOL #94/38 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

Key Word: Sterilization

Study Objective: Among women in a military population who seek reversal of tubal ligation, to determine what factors they identified as responsible for their desire to overturn a permanent procedure.

Technical Approach: Questionnaire

Progress: Study was terminated, Principal investigator ETS'd. OB/GYN staff was interested in continuing with study.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): CPT Robert Zabenko

PROTOCOL TITLE: Management of Inflammatory Cytologic Abnormalities Detected by Papanicolaou Smears: A Randomized, Double Blinded Prospective Study

PROTOCOL #96/08 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): JW Carlson, P Schmagel, E Nolen

Keywords:

Study Objective: To prospectively evaluate the efficacy of intravaginal metronidazole versus an intravaginal control gel for the treatment of inflammatory atypia diagnosed on cervical cytology.

Study design: A prospective, randomized, double blinded trial of intravaginal metronidazole treatment versus an intravaginal control will be conducted on eligible patients who have inflammatory abnormalities on their Pap smears.

Progress: 30-40 subjects have been enrolled in study. Once all subjects have been accrued data will be analyzed.

DEPARTMENT OF PATHOLOGY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): 1LT Steve D. Mahlen

PROTOCOL TITLE: Evaluation of PCR for Use in Diagnosis of Microbiologic Infections

PROTOCOL #95/39 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): M Lund

Keywords:

[redacted]

Technical Approach: Primers for specific infectious agents will be manufactured in DCI using

DEPARTMENT OF PEDIATRICS

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): COL Alva W. Atkinson

PROTOCOL TITLE: Retrospective Analysis of the Association between Attention Deficit Disorder and Central Auditory Processing Problems

PROTOCOL #92/01 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): R Dennis, MC Knott, D Penow

Key Words: ADD, CAPP

Study Objective: Two hyptheses will be addressed: (1) Central auditory processing problems (CAPP) occur in high frequency (>20%) among patients diagnosed with Attention Deficit Disorder (ADD) and (2) the incidence of CAPP in ADD will be represented equally among the subtypes of ADD (ADD with hyperactivity and ADD without hyperactivity).

Technical Approach: The Medicall records of patients assessed by Developmental Pediatrics Clinic for ADD and by Audiology and Speech/Language Clinics during 1989-1990 will be reviewed. Data will be collected for age, grade, diagnoses, auditory and language evaluation

DEPARTMENT OF PEDIATRICS

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Kelly Faucette

[redacted]

DEPARTMENT OF PEDIATRICS

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Wayne E. Hachey

PROTOCOL TITLE: Microtechnique For Determination of Prothrombin Time (Pt) and Activated Partial Thromboplastin Time (Aptt) in Neonates Compared to Conventional Analysis

PROTOCOL #96/13 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): SA Remich

Key Words: Coagulation profile, neonate

Study Objective: This study will evaluate whether the results from the Biotrack 512 PT/Ptt Coagulation System are comparable to the classic PT/APTT tests in neonates.

Study design: This will be a prospective, non-randomized, non-blinded study. Routinely, cord blood is obtained from the placental umbilical cord immediately after delivery. A section of the umbilical cord is wiped to remove any maternal blood, and one of the umbilical vessels is entered with a needle attached to a 10 or 20 ml syringe. The blood sampling will take place within 20 min. of delivery and the sample will be brought to laboratory immediately thereafter. Blood is then aspirated from the umbilical vessel. This blood is fetal/baby blood, not maternal blood. The placenta and attached umbilical cord are then discarded. This cord blood is used for several routine studies, but these do not include PT/APTT. Usually, more blood is drawn from the cord than is needed for the routine studies, and there is usually a substantial volume of blood remaining in the placenta and umbilical cord when they are discarded. This study would utilize this extra blood for evaluating the correlation between the classic laboratory method for PT/APTT determination and the real-time, microtechnique using the Biotrack 512 PT/Ptt Coagulation System.

At the time the cord blood sample is drawn for routine studies, an extra 3 ml of blood will be drawn for use in this study. A large drop of blood will be placed on each of the 2 Biotrack 512's, one for PT and one for APTT determination. The remaining blood (approximately 2.5 ml) will be placed in a pediatric buffered sodium citrate tube and sent to the lab for determination of PT and APTT. The results will be analyzed to determine if there is a statistical difference between the two methods. A quality control record will be maintained as per the Biotrack, Inc. recommendations.

By using cord blood, we will be sampling in the immediate post-partum/early neonatal period. This is important, because there are changes that take place in the blood during the first few weeks and months of a child's life. Since most acquired neonatal coagulation problems occur in the first 1-2 weeks of life, testing cord blood will give an accurate reflection of neonatal coagulation, at least in healthy neonates. Using cord blood also has the benefit of not requiring phlebotomy from a patient and not requiring any additional procedures except for handling and running the samples.

If any samples yield abnormal results, these results will be discussed with Dr. Kelly Faucette, Pediatric Hematologist, WBAMC, and appropriate follow-up tests performed.

Progress: This study was postponed until November 96 but will be conducted with the help of the Boehringer Mannheim Corp. manufacturer of the CoaguChek Plus whole blood monitoring device that measures Pt and APTT.

DEPARTMENT OF PEDIATRICS

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Wayne E. Hachey

PROTOCOL TITLE: Determinationof the Effect of High Frequency Oscillatory Ventilation on Cerebral Blood Flow in a Piglet Model

PROTOCOL #96/22A STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): SA Remich

Key Words: cerebral blood flow, high frequency ventilation

Study Objective:
The null hypothesis states that there will be no change in cerebral blood flow while receiving high frequency ventilation during both normal degrees of expansion and hyperexpansion.

Study design: 10 Newborn piglets, 1-2 weeks of age will be utilized to answer the question: will cerebral blood flow be affected by high frequency ventilation when used appropriately and under conditions of hyperventilation. Each animal will act as its own control. Each animal will be premedicated with Ketamine and Valium then will be anesthestized with Chloralose/urethane and artificially ventilated. Conventional ventilator settings will be adjusted to maintain arterial blood gas determinations within normal limits. A catheter will be inserted in the femoral artery for blood pressure and blood gas monitoring. A thermistor will be inserted in the contralateral femoral artery for cardiac output monitoring. Additionally, the subclavian vein will be cannulated as an injection site for thermal dilution measurements. The external carotid and occipital artery are then both ligated. This results in the modified common carotid providing cerebral flow. An electromagnetic flowmeter probe is then fitted around the right common carotid artery. A feeding tube will also be inserted in the esophagus to monitor transpulmonary pressures. Baseline measurements to include precerebral blood flow (common carotid), blood pressure, transpulmonary pressure, heart rate, cardiac output and arterial blood gas determinations will be obtained. Arterial carbon dioxide levels will be kept constant (within 5mm Hg) thorough out the study. A chest radiograph will be obtained to determine the degree of expansion. The piglet will then be placed on high frequency ventilation. The initial mean airway pressure will be equal to that while on conventional ventilation. Inspiratory time to equal 33%, amplitude adjusted to provide chest vibration and no significant change in $PaCO_2$. Chest expansion will be determined by chest radiograph, and change in chest wall diameter. Baseline measurement will be repeated. The mean airway pressure on the high frequency ventilator will then be increased so that diaphragmatic excursion, on chest radiograph, increases by at least 2 anterior ribs. Baseline measures will be repeated. High frequency support will then be decreased to the previous, prehyperexpansion level followed by a repeat of baseline measurements. Finally, the piglet will be returned to conventional ventilation with a repeat of baseline of baseline measurements. The piglet will then be euthanized.

Progress: This study is currently active.

DEPARTMENT OF PEDIATRICS

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ William Raszka

PROTOCOL TITLE: Knowledge of Immunization Practices Among Pediatric Health Care Providers in Medicall Centers

PROTOCOL #94/35 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): NA

Keywords: Immunization, Health Care Providers

Study Objective:
1) To determine the body of knowledge regarding current pediatric immunization practices that pediatric housestaff have at each level of training.
2) To determine the body of knowledge regarding current pediatric immunization practices that pediatric staff have by type of specialty.
3) To determine if housestaff from military programs are any different from civilian programs.

Technical Approach: Survey using a validated survey form. The survey was validated by administering it to pediatric infectious disease specialists and general pediatricians not participating in the study.

Progress: Dr. Raska has left the institution. This protocol has been administratively terminated as no one in the Dept. of Pediatrics has continued it.

DEPARTMENT OF PEDIATRICS

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): LTC Robert Sayers

PROTOCOL TITLE: Parents Opinions about Disorders of Vigilance in their Children with Attention Deficit Disorder

PROTOCOL #91/55 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): AW Atkinson

Key Words: Primary Disorder of Vigilance (PDV), Attention Deficit Hyperactivity Disorder

Study Objective: Through the use of a parent questionnaire, determine the incidence of symptoms of Primary Disorder of Vigilance (PDV) in a population previously diagnosed with Attention Deficit Disorder (ADD) or being evaluated for ADD. Furthermore, this project will seek to differentiate this symptom cluster (PDV) as either a unique diagnosis or a subtype of ADD.

Technical Approach: The Developmental Pediatric Clinic at WBAMC follows approximately 180 patients with the diagnosis of ADD. Patients who are taking medication for ADD are seen in clinic at least every three months and parents come in for a brief interview on progress and refill every month. During one of these routine follow-ups, the parent will be asked to complete a questionnaire which addresses the major criteria for PDV for both the child and his/her parents. These criteria are taken directly from the article "Primary disorder of vigilance: A novel restlessness, and sleepiness" by Weinberg describing this "new" disorder.

Progress: .Number of subjects entered in the study is 120. At this time data collection has been completed but data analysis is still ongoing.

DEPARTMENT OF SURGERY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Chester C. Buckenmaier

PROTOCOL TITLE: Comparison of Current Antiadhesive Treatments in the Rat Tensiometer Model

PROTOCOL #95/61A STATUS: Completed

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): None

Keywords: Antiadhesive, rat

Study Objective To compare and contrast the various current methods of adhesion prevention following laparotomy utilizing the objective rat tensiometer model for evaluating adhesion formation.

Technical Approach: Abdominal adhesions following laparotomy develop in two-thirds of patients and are the most common cause of acute and recurrent small bowel obstruction (Thompson et al 1989). Peritoneal adhesion formation represents a significant problem for the surgeon, not only because of the morbidity associated with adhesive disease but also the heightened difficulty inherent with subsequent abdominal operations in patients with extensive adhesion formation. Historically, a number of antiadhesive agents have been proposed and tested with a spectrum of success. Unfortunately these antiadhesives have been tested on a number of different animal models making comparison of the various agents difficult. Additionally, most of the models have utilized subjective scoring criteria when
evaluating adhesion formation which is inherently biased. In the proposed study the most successful antiadhesive agents, as defined in the current literature, will be compared utilizing an objective rat tensiometer model for adhesion formation as described by Harris *et al* 1995.

Progress: This study has been completed.

DEPARTMENT OF SURGERY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Chester C. Buckenmaier

PROTOCOL TITLE: Comparison of Current Antiadhesive Treatments in the Rat Model Part II

PROTOCOL #96/33A STATUS: Completed

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): None

Keywords: Antiadhesive, rat

Study Objective: To compare and contrast current methods of adhesion prevention utilizing efficacious treatments determined from prior research and commercially available products for adhesion prevention. The objective rat tensiometer model for evaluating adhesion formation will be employed in this study. Significant variability in the ability of antiadhesive agents to prevent adhesions in the rat tensiometer model exists. One agent is superior in adhesion prevention.

Technical Approach: Sprague-Dawley rats weighing 240 to 280 gm will be anesthetized with intraperitoneal injection of pentobarbital Na 50 mg/kg. When anesthesia has been established the rat's abdomen will be clipped with surgical clippers and prepped with povidone iodine. Laparotomy will then be performed with a low midline incision of 5 cm. The cecum will then be identified and abraded with a scalpel until punctate bleeding is observed. A peritoneal defect will then be created in the anterior peritoneum overlying the cecum with a 0.8 cm punch biopsy. Next, a series of four ischemic buttons will be created in the left paracolic gutter. The ischemic buttons will be created by picking up a small "button" of peritoneum adjacent to the paracolic gutter with fine forceps and ligating the base with 3/0 vicryl. The peritoneal cavity will then be bathed in 10 cc of test solution. The peritoneal cavity will then be closed with a running 2/0 coated dexon suture, the skin will be closed with surgical staples. The rats will then be allowed to recover and will be cared for under standard animal facility protocols. On day 7 the rats will again be anesthetized as described above.

A second laparotomy will be performed and the force required to separate the adhesions between the cecum and the 1 cm peritoneal wall defect will be measured with the tensiometer. Additionally, the presence or absence of adhesions to the four ischemic buttons will be noted for a score of 0 to 4. The animal will subsequently be euthanized as described above.

Progress: This protocol has been completed. This protocol is the second part of protocol #95/61A.

DEPARTMENT OF SURGERY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): LTC Dale A. Bauer

PROTOCOL TITLE: Accuracy of Orthognathic Evaluation Using Telemedicine Technology

PROTOCOL #96/15 STATUS: Completed

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Ringgold, R Jordan, AE Pusateri

Keywords: Telemedicine

Study Objective: To prove that telemedicine technology is reliable and accurate for prelmiinary orthognathic evaluations. If this proves to be true, then OMF Surgeons can have some degree of confidence in evaluating other types of patients, i.e., trauma, infections, pathology, post operative evaluation, and reconstruction.

Study Design: This will be a cross-over design. Subjects will be assigned randomly and equally to receive either a teledentistry examination or a traditional examination on the first day. On the second day, eachsubject will reeive the remaining examination. Each subject will be examined in this order by the first oral surgeon and again in the opposite order by the

[redacted]

oral surgeon.

DEPARTMENT OF SURGERY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): CPT Albert L. Chorens

PROTOCOL TITLE: A Prospective Randomized Comparison of Inguinal Herniorrhaphy : Laparoscopic Extra-Abdominal Pre-Peritoneal vs. Open Tension Free vs. Open Traditional

PROTOCOL #95/12 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): B Whitlow, SP Hetz, J Holcomb

Keywords:

Study Objectives:The principal objective is to determine which of the three mentioned techniques offers the lowest rate of recurrence, the least morbidity, and the least period of convalescence before a return to the patient's pre morbid baseline.

Technical Approach: Those patients who present to the General Surgery Clinic, who on physical exam by a staff General Surgeon, demonstrate an inguinal hernia (s) will be the target population. From this group, the patient deemed to be a surgical candidate will be advised of the herniorrhaphy protocol.

The surgical candidate with an inguinal hernia(s) will have the risks and benefits of herniorrhaphy explained. Additionally, the goal of the study protocol will be explained , as will each arm (surgical technique) of the protocol be explained. An opportunity for patient's questions regarding the above will be given. At this time, the patient will be given a Volunteer Agreement Affidavit for review and signature, if patient is so inclined to participate.

The patient who agrees to participate in the study protocol, will be scheduled for a return appointment in the General Surgery Clinic. At that time, additional questions by the patient may be answered regarding the herniorrhaphy protocol. Formal enrollment into the protocol will be completed. Actual blind prospective randomizing of patient into protocol treatment arm will be done. Blind randomization is desired, in order to decrease the incidence of patient subjectivity and patient bias regarding herniorrhaphy procedure and potential for decreased participation due to same. The patient will be previously counseled to this condition of protocol participation. The scheduled date of surgery will be finalized.

Blind prospective randomization will be performed by assignment of patient via blind randomization numbers table to a previously determined herniorrhaphy treatment limb (procedure).

The three treatment limbs of the inguinal herniorrhaphy protocol will be as follows:

i) Laparoscopic extra-abdominal pre-peritoneal herniorrhaphy with prolene mesh as described fundamentally by McKernan (11) with modification by Phillips and Carroll (12).

ii) Tension free open herniorrhaphy with prolene mesh as described by Lichtenstein (14).

iii) Traditional open herniorrhaphy as variously described by the standard Bassini, standard McVay, standard Shouldice repairs.

Performance exercise testing via straight leg raises will be determined pre-operatively as an objective independent variable assessing the patient's pre morbid baseline activity level. A post-operative assessment will also be conducted to determine the patient's return to baseline activity as an indicator of *return to normal activity* (9).

Bilateral hernias. Pt assessed with bilateral inguinal hernias on exam by staff General Surgeon will not be excluded. Instead , the patient will have the bilateral hernias repaired via a blind randomized treatment limb of the herniorrhaphy protocol as follows:

i) If randomized to laparoscopic treatment limb- Bilateral repairs will be completed at same operation.

ii) If randomized to either tension free or open traditional repair treatment limb- Patient will have the more subjectively problematic hernia repaired, initially. At that time in post-operative course, the patient is able to return to his pre-morbid activity baseline as assessed by the performance exercising testing as defined above, patient will undergo repair of remaining inguinal hernia by the same treatment limb method.

Recurrent hernias. A recurrent hernia will be defined in the following fashion: presence of an inguinal hernia (as detected by physical exam by a staff General Surgeon), in a patient who was previously assessed as having an inguinal hernia on the ipsilateral side and who has undergone subsequent herniorrhaphy of same. Distinction will be made between *early* and *late recurrence* (15). Early recurrence will further be defined as a hernia that is present within 2 years of ipsilateral herniorrhaphy. Early recurrence will imply technical failure of repair. Late recurrence will further be defined as a hernia that is present 2 years or greater since ipsilateral herniorrhaphy. Late recurrence will not be attributed to technical failure, rather late recurrence will be attributed to an intrinsic disorder of the patient's own physiology (10).

i) Early recurrence of inguinal hernia as assessed by a staff General Surgeon will be re-entered into herniorrhaphy protocol in a blind randomized fashion as above.

ii) Late recurrence of an inguinal hernia as assessed by a staff General Surgeon will be re-entered into herniorrhaphy protocol in a blind randomized fashion as above.

Patients w/ recurrence of inguinal hernia as defined above, unwilling to re-enter herniorrhaphy protocol will be dropped from protocol at that point in time. Further surgical consultation will be offered to these patients, outside the parameters of the herniorrhaphy protocol.

Convalescence leave. All patients in protocol will receive a defined amount of convalescence leave for recovery from his herniorrhaphy procedure. Patients randomized to either the laparoscopic extra-abdominal pre-peritoneal procedure or the open tension free repair, will receive 7 days of convalescence leave from date of operation. The patients in these above treatment arms will have no restrictions of activity post-operatively. Patients undergoing traditional open repair, will receive 7 days of convalescence leave with restrictions of activity to include no lifting greater than 10 lbs., patient may walk at own pace and distance (no running or jogging), no other form of purposeful abdominal straining.

Progress: Since December 1995 through October 1996 we have accrued 160 patients in a prospective randomized comparison of inguinal herniorrhaphy, laparascopic properitoneal versus open tension free versus open traditional methods. This study has been well received and integrated into the General Surgery Service, with Dr. Chorens acting as the senior resident in charge of the study, supervised by myself, but essentially with the entire residency program, both residents and staff contributing to the study. The randomization of patients has proceeded very smoothly. We are in he midst of doing an interim analysis of the data since there are a little over 50 patients in each arm. It is my impression from seeing the patients back in the clinic postoperatively that the laparascopic repair takes somewhat longer than the other open repairs, however, those patients have less postoperative pain based on their Visek pain scores and return to normal ambulation, activities and leg lifts sooner than the other open repairs. The open traditional approach seems to take longer to get back to normal physical activity. These are subjective comments at this time, however, based upon personally examining and seeing probably two-thirds of the patients.

There has been one case of one complication in a laparoscopic hernia repair done on protocol directly attributable to the laparoscopic hernia technique of a bladder rupture by the balloon dissector. There is in a patient with previous prostate surgery. Communication with the company reveals four prior known episodes similar to this of the approximately 200,000 laparoscopic herniorrhaphies performed nation-wide with this balloon. We are in the process of communicating this information with this recent event through the appropriate channels.

This project is in compliance with the requirement that there is no unnecessary duplication that I know of nor does the company know in any other prospective randomized study comparing three types of hernia repairs, with minimal exclusions with the Visek pain scores and leg lift follow-ups, giving an objective as opposed to subjective assessment of when the patients are able to return to their preoperative level of physical activity.

DEPARTMENT OF SURGERY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): CPT Robert Craig

PROTOCOL TITLE: *In vivo* Biodistribution of Radiolabeled Fibrinogen-Coated Lecithin/Cholesterol Vesicles in the Anesthetized Rat Model

PROTOCOL #95/58A STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): H Holcomb, S Bhattacharyya, P Alsbugh

Keywords:

Study Objective: Fibrinogen-coated liposomes will have an identical in vivo biodistribution as that of non-fibrinogen-coated liposomes.

Technical Approach: This study will attempt to determine how a new chemical compound, designed to lessen the loss of blood after a major injury, is distributed throughout the body. The new experimental compound consists of a fatty carrier portion linked to the blood clotting portion. A total of thirty rats will be divided into three groups of 10 rats each. Under anesthesia, one group will have the new compound with a low level and short-lived radioactive substance attached to it injected into the blood stream. Another group will be injected with only a radioactive labeled fatty carrier portion of the compound. The last group of ten rats will be injected with only the radioactive substance without the experimental compound. The images obtained by the radioactive scanning will be compared to determine the distribution of the experimental compound in the body. Tissue specimens from the euthanized rats will be examined for gross as well as for microscopic abnormalities.

Progress: The fibrinogen-coated vesicles have been developed. Animal phase of this study has not been started.

DEPARTMENT OF SURGERY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Vermon S. Esplin

PROTOCOL TITLE: The Use of Pneumatic Tourniquet in Extremity Surgery Following End-to-End Arterial Anastamoses in the Caprine Model.

PROTOCOL #95/26A STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): SD O'Donnel, RA Harris

Keywords:

Study Objective: The objective of this study is to evaluate the effect of the use of a pneumatic tourniquet has on a vascular repair when the tourniquet is used proximal to that repair during the immediate postoperative time period (one to fourteen days).

Technical Approach: The use of a tourniquet after repair of blood vessels has not been properly studied. Unfortunately, many times when repair of a blood vessel in an arm or leg is needed, other problems are also present that need surgery. The usual technique to repair these problems requires the use of a tourniquet to keep bleeding from obstructing the view of the surgeon. Healing of the blood vessel tissues after repair is a process that gives the repair strength over time. Since placing a tourniquet on an arm or leg will pool blood in the blood vessels, pressure can build up over a short period of time and break the repair of the blood vessel. This protocol is an attempt to determine in the goat model the shortest period of time after repair of a blood vessel than will allow the use of a tourniquet without damage to the repaired blood vessel. By determining the shortest period of time required, a patient can have other problems repaired in a timely manner that may well increase function, or even use, of the arm or leg in the future.

Progress: This study is currently inactive but will be continued by MAJ Vermon S. Esplin, Hand Surgeon. Review will be made of complete protocol and amendments will follow. No specimens have been done yet. Changes will follow and be discussed with the IACUC and attending veterinarian.

DEPARTMENT OF SURGERY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Steven Gange

PROTOCOL TITLE: Doxazosin vs. Transurethral Electrical Vaporization of the Prostate (TEVAP)

PROTOCOL #96/20 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): M Bagg, TS Gormely

Key Words:

Study Objective:
The objective of the study is to determine the safety and effectiveness of two treatments for the condition of Benign Prostatic Hypertrophy (BPH). The treatments used will be Doxazosin and TEVAP. If Doxazosin proves to be as clinically effective as TEVAP it would potentially obviate the need for anesthesia and surgery. WBAMC's role in this study is recruit, evaluate and treat patients with BPH. Data will also be collected and analyzed and submitted to Texas Tech University.

Study Design: This is a prospective, randomized study conducted at Texas Tech University Medical Center, Lubbock, Texas in which approximately 80 patients with moderate to severe symptoms of BPH will be randomized to either transurethral electro-evaporation of the prostate (TEVAP), or medical therapy with Doxazosin. Patients will be followed for a minimum of one year following BPH intervention.

Progress: No progress was reported principal investigator left WBAMC. No one in the Urology Service was interested in continuing this study.

DEPARTMENT OF SURGERY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): LT Georgia Gil

PROTOCOL TITLE: Epidural Morphine Sponge Analgesia for Lumbar Diskectomy

PROTOCOL #96/21 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): W Stevens, JJ Leech, DW Cockerill

Keywords: Epidural morphine, analgesia, gelfoam sponge, lumbar diskectomy

Study Objectives: Determine the post-operative analgesic efficacy of methylprednisolone acetate/Morphine impregnated gelatin sponge depository applied in post-diskectomy laminectomy defect.

Study design: Prospective, Randomized, Placebo Controlled Double Blinded. Lumbar diskectomy will be carried out by the usual fashion. Subjects will be assigned randomly to treatment using a random numbers table.[28] After excision of disk material, a gel foam sponge will be trimmed to fit the laminectomy defect. This will be soaked in 60mg of Methylprednisolone. It will then be injected with either 4 mg of preservation free Morphine or 4cc of preservative free normal saline. The morphine or saline would be supplied by the pharmacy. It will arrive in the OR encoded. The code number will be maintained by the pharmacy and the code will not be broken until completion of the study. The sponge will be placed in the laminectomy defect directly on the cord. Closure will be carried out in the usual manner. Kits containing study paperwork will be supplied to the associate investigator by the principal investigator.

Post-operatively, patients will be placed on demand only patient controlled analgesic (PGA) pumps. Amount of morphine consumed will be recorded on the standard PCA chart. PCA will be discontinued as soon as pain subsides to a level which can be treated with oral medication. This will be a clinical decision by the surgeon.
Percocet, one or two by mouth every 3 to 6 hours, will be prescribed to be used on an as needed basis. Patients will receive Phenergan, 25mg IM every 4 to 6 hours if needed for nausea. Regular 325mg Tylenol will also be available on an as needed basis.
Patients will be discharged with Percocet, dosed as above, and Tylenol to be used on an as needed basis.

Pre-operative questionnaire on pain medication use, McGill questionnaire and analog pain scales for back pain and radicular pain will be administered by the evaluating physician at time of preoperative evaluation. This will remain with the in patient chart paperwork. Post-operatively, analog pain scales will be administered by nursing staff at 4 and 8 hours post-op. Analog and McGill pain scales will be administered by nursing staff on days one, two and three post-op. On day 3 post-op, patients will complete an additional questionnaire addressing pain medication use after discharge and overall satisfaction and functional status. This will be administered with the pain scales. Many patients will be discharged prior to post op day 3. At time of discharge, the patient will take any remaining questionnaires and complete them at home on the appropriate day. The patient will return them to the associate investigator at the first follow up. The associate investigators will maintain these questionnaires until they are collected by the principal investigator.

Progress: No progress has yet been reported by PI, she has just recently started this project due to a 5 month training program she attended in Spokane, WA. Start date is 1 Jan 97.

DEPARTMENT OF SURGERY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): LTC Thomas S. Gormley

PROTOCOL TITLE: Comparative Study of the Clinical Efficacy of Two Dosing Regimens of Eulexin

PROTOCOL #95/37 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): L Maldonado

Keywords: D_2, CAP

Study Objective: The objective of this study is to compare the clinical effectiveness of a new dosing regimen 500 mg (QD) for administering flutamide to the currently indicated dosing regiment of 250mg q 8 hours according to:

Percent of patients normalizing PSA

Quality of life differences between the two Regimens.

Technical Approach: This is a Phase IV, multicenter trial in which 400 available patients with *de novo* Stage M metastatic prostate cancer will be randomized to one of two treatment groups.

Group 1: flutamide, 250 mg Q8H + LHRH/orchiectomy

Group 2: flutamide, 500 mg QD + LHRH/Orchiectomy

Progess: Five patients have been enrolled in study. No adverse reactions have been reported this year. The estimated completion extended to Nov 97.

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[redacted]

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DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): LTC Stephen P. Hetz

PROTOCOL TITLE: Resident Training in Laparoscopic and Open Stapling Techniques

PROTOCOL #91/13A STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): W Bowland

Key Words: Laparoscopic Training

Study Objective: The objectives are to teach the surgical staff and residents proper thoracic and abdominal laparoscopic procedures utilizing stapling instruments and suturing techniques and proper open stapling techniques utilizing the multitude of gastrointestinal staplers, including the TA, GIA, EEA instrumentation, the LDS instrument and the Liga Clip Appliers.

Technical Approach: Both video laparoscope and open surgical training techniques will be conducted in the porcine model. The experimental design is such that one or both of the techniques will be conducted on each animal. When both laparoscopic and open techniques are utilized, the laparoscopic techniques will precede the open procedures. The determination of the techniques to be conducted will be done at the time of the training session and will be dependent upon the knowledge and expertise of the residents and staff being trained. After anesthesia induction, the following procedures will be conducted:

(1) Video laparoscopic - Abdominal: cholecystectomy, gastrectomy, small bowel resection, nephrectomy, hysterectomy, splenectomy and partial hepatectomy. Thoracic: esophagectomy, pulmonary resections and vagotomies will be performed utilizing the various stapling instruments and liga clips.

(2) Laparotomy (Open) - Abdominal: A midline incision from the xiphoid process to the pubis will be made. Then a multitude of gastrointestinal staplers, including the TA, GIA, EEA instrumentation, the LDS instrument and the Liga Clip Appliers will be utilized to complete end-to-end, side-to-side colon and small intestinal anastomosis. Additionally, anastomosis will be completed between portions of the small intestine; from the small intestine to stomach and colon; and between the colon and rectum. Transection of the stomach, colon and small intestine will also be performed. Pulmonary: Transection of pulmonary tissue, bronchi, pulmonary arteries and veins will be performed utilizing the various instruments through an intercostal incision.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or [redacted]

DEPARTMENT OF SURGERY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): LTC Stephen P. Hetz

PROTOCOL TITLE: Certification Training: Advanced General Surgery Laser Laparoscopic Procedures in the Porcine Model

PROTOCOL #91/15A STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): W Bowland

Key Words: Laser Laparoscopy Training

Study Objective: To provide training and certification of General Surgery Surgeons in laser laparoscopic cholecystectomy, hernia repair, and appendectomy. This training will enable them to develop the proficiency required to perform these operative procedures in human patients.

Technical Approach: The animals' food will be withheld for a period of 18 hours prior to surgery. The pigs' hair will be clipped from the abdomen. The animals will be placed in dorsal recumbency. After the skin is prepped, an insufflation needle will be inserted and the abdomen will be filled and maintained with 15 mm Hg pressure of CO_2. A trocar/cannula will be placed near the umbilicus for introduction of the video laparoscope which will enable monitoring of the procedure on a video screen. Two to three additional trocars/cannulas will be placed for introduction of laparoscopic graspers, scissors, laser fibers, etc. The cystic duct and artery will be bluntly dissected free, double ligated or clipped, and transected. The gallbladder will be dissected free from the liver bed by sharp, blunt, electrosurgical and laser techniques. Once free from hepatic parenchyma, the gallbladder will be approximated to the body wall, decompressed and pulled through one of the central trocar puncture sites.

Other advanced laparoscopic procedures will include hernia repair and appendectomy. Laparoscopic cannulas will be repositioned as necessary for subsequent procedures to

DEPARTMENT OF SURGERY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): LTC Stephen P. Hetz

PROTOCOL TITLE: Advanced Trauma Life Support Training in the Small Ruminant (Ovine or Caprine Animal Model

PROTOCOL #92/18A STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

Keywords: ATLS Training

Study Objective: This training will enhance the physician's capabilities of administering advanced trauma life support procedures to patients with emergency medical conditions which require establishment of airways, venous access, and chest and abdominal trauma management.

Technical Approach: The Advanced Trauma Life Support (ATLS) training program is designed for physicians who are not primarily responsible for managing the critically injured patient on a day to day basis. The American College of Surgeons (ACS) Committee on Trauma defines

DEPARTMENT OF SURGERY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): LTC Stephen Hetz

PROTOCOL TITLE: The Use of Marcaine in the Prevention of Post Operative Pain in the Laparoscopic Cholecystectomy Patient

PROTOCOL #93/56 STATUS: Completed

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): SP Hetz, JH Chiles

Key Words: Marcaine Pain, Laparoscopic, Cholecystectomy

Study Objective: This study will determine if the duration of the procedure, the anesthesia of the diaphragm and the anesthesia of the surgical site reduce post operative pain.

Technical Approach: The study will be a single center, double-blind study which will be prospective in nature.

Progress: 100 subjects were entered in the study. Fifteen subjects withdrew secondary to conversion to open technique or lost to follow-up. There were no noted adverse reactions. Study has been completed.

DEPARTMENT OF SURGERY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ(P) John B. Holcomb

PROTOCOL TITLE: Dry Fibrin Glue for the Repair of Severe Liver Injury in the Anesthetized Porcine Model (*Sus scrofa*)

PROTOCOL #96/04A STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): AE Pusateri, SP Hetz, RA Harris

Keywords: Dry fibrin glue, repair severe liver injury

Study Objectives: To evaluate the efficacy of dry fibrin glue in maintaining hemodynamic stability and decreasing hemorrhage in a severe liver injury model. Fibrin glue, applied in a dry powder form, can effectively control hemorrhage from a severe liver injury.

Technical Approach: This study will be a split-plot design with animals assigned randomly to treatments. A total of 60 pigs will be used in this study. The initial 20 pigs will be used to refine research procedures. From 2 to 5 animals will be used in each proposed group to refine procedures. None of the procedures, including injury, packing, and delivery of fibrin sealant have been done. The development of injury and packing should proceed rapidly. However, delivery of dry fibrin sealant to a liver injury is unique and will require some manipulation. The following randomization procedure will be used for the 40 pigs which will be assigned to treatment groups. Pigs will be tagged, weighed, and ordered on the basis of increasing BW. Pigs will then be assigned randomly to treatments in permutations of 4, in order of increasing BW. The resultant sets of 4 pigs will then be randomly assigned to week of treatment. This randomization procedure will be repeated for each group of pigs as the pigs are received at the laboratory animal facility.

A control group of 5 animals will be studied, with no treatment after liver injury is created. A sham control group will be studied (5 animals) that will document the effects of splenectomy and fluid resuscitation without injury on the animals. This sham control group will be a survival model. This control group (both sham and no treatment) will comprise Group 1 in the study. Each animal will have placement of a large bore central venous line and an arterial line for monitoring of heart rate, mean blood pressure and effects of fluid resuscitation. These lines will be placed after the pigs are anesthetized. Blood will be sent for a coagulation profile (PT/PTT, fibrinogen). At this point a midline laparotomy and splenectomy will be performed. A standardized liver injury will be created and blood pressure monitored until the mean arterial pressure is 25% lower than initial baseline. At this point intravenous fluid

[redacted]

assessing the liver injury to determine if the fibrin glue has in fact sealed the wound. Histolgic analysis of the clot/fibrin sealant/liver parenchyma interface will be performed.

Progress:

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DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Darwin D. Karr-Peterson

PROTOCOL TITLE: A Comparison of Antiseptic Impregnated Central Venous Catheters and Standard Central Venous Catheters in Catheter Related Bloodstream Infection

PROTOCOL #95/29 STATUS: Terminated

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): B Burlingame, SP Hetz, J Holcomb

Keywords:

Study Objective: The purpose of this study is to determine whether or not the use of AICVC's will result in fewer CRBSI's by comparing the infection rate between standard CVC's and AICVC's being used in the same intensive care unit during the same time period.

Technical Approach: This study will be confined to WBAMC surgical intensive care patients,

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DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): Mary C. Knott

PROTOCOL TITLE: Morphosyntactic Development in Specific Language Impairment

PROTOCOL #96/19 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): Julia A. Eyer, Phd, UTEP

Keywords: Fast mapping, specific language impairment, morphological development

Study Objective: This study looks at children's understanding and use of certain grammatical forms. Current theory suggests that grammatical weaknesses may limit the child's ability to learn new words rapidly, especially regarding the differences between word classes such a nouns and verbs. This study examines differences between preschool children with language impairments and normally-developing peers. William Beaumont Army Medicall Center will be involved in the referral of appropriate children for participation and in providing space for testing.

Study Design:

The project will involve approximately six sessions, each of about one hour in duration. These sessions will take place in the Speech Pathology Section, within Audiology/Speech-Pathology Clinics, Otolaryngology Services of WBAMC, or if the parent prefers, in the child's home. During these sessions, the child and examiner will interact informally while playing with toys and books in order to allow for observation of the grammatical forms the child uses in spontaneous speech. In addition the child will participate in tests of his/her language, speech, and hearing abilities. For example, the child will be presented with pictures whose descriptions contain certain sounds, words, or sentences of interest to this study. The child will be encouraged to talk about these pictures with the examiner and to point to the pictures in response to questions.

Progress: Children classified as having a specific language impairment (SLI) are those who exhibit a significant delay in language acquisition while demonstrating normal abilities in the development of cognition, hearing, moor skills, and social interaction. Especially difficult for these children are areas of grammar surrounding the very system. Current theory suggests that grammatical weaknesses may limit the child's ability to learn new words rapidly, especially regarding the difference between word classes such as nouns and verbs.

The on-going study described here examines the differences between pre-school children with SLI and normally-developing peers matched for language skills (i.e., younger group) and peers matched for chronological age. These three groups are being exposed to novel nouns and verbs in contexts that require comprehension of fine grammatical detail (i.e., a and the vs. the past tense ed) to differentiate between the two classes.

As of September 1996, six experimental subjects have completed the research protocol. An additional two subjects failed to meet inclusion criteria and were terminated following the initial testing session. These eight children included those recruited from WBAMC as well as those from the public school liaisons approved via the UTEP Institutional Review Board. Additionally a survey of WBAMC patient folders has yielded a roster of

DEPARTMENT OF SURGERY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Thomas McCrorey

PROTOCOL TITLE: A Prospective Randomized Clinical Controlled Trial of Laparoscopic Vs. Open Appendectomy

PROTOCOL #95/13 STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): S Hetz

Keywords:

Study Objective:A. Compare the postoperative courses
B. Date of discharge
C. Time until return of full activity

[redacted]

E. Wound infection and complication rate
F. The rate of postoperative abscess specifically.

Technical Approach: All patients presenting to the surgery service with a diagnosis of acute appendicitis will be offered randomization to either the open or laparoscopic arm of the trial. Laparoscopy will be pursued in all in whom it is technically possible.The only exclusion will be made for women in the third trimester of pregnancy, under the assumption that the laparoscopic technique is more risky than the open. Conversion to open appendectomy will not be done for other reasons, including for the ruptured or gangrenous appendix.

[redacted]

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DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): CPT Chet Morrison

PROTOCOL TITLE: The Effect of Timing on the Efficacy of Pneumococcal Vaccine in the Post-Splenectomy Rat Model

PROTOCOL #96/07A STATUS: Completed

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): MA Schreiber, AE Pusateri, BC Veit, RA Harris

Keywords:

Study Objective: To prove that the response to polyvalent pneumococcal vaccine is not affected by the post-splenectomy interval.

Technical Approach:

Experiment 1: The purpose of the first part of the experiment will be to determine the appropriate dosing of the pneumococcus organism and of the polyvalent pneumococcal vaccine. A preliminary non-statistical study will be performed in order to determine the range of inoculum indicated for pneumococcal injection to produce imminent death in 50-75% of the animals (LD50-75). This will consist of 15 rats divided into 3 groups. The rats will undergo splenectomy and receive pneumococcus intravenous injection 1 week postoperatively. Group 1 will receive 10^3 organisms, Group 2 will receive 10^5 organisms and Group 3 will receive 10^7 organisms. This dosing range was determined by prior trials revealing that injection of 10^5 organisms in splenectomized rats produces a 65% mortality (5).

Based on the results of the preliminary study a second study will be designed to achieve statistical significance. This study will be composed of 4 groups of 17 rats each. The groups will consist of a control group which will undergo splenectomy and then receive intravenous saline injection 7 days postoperatively and 3 treatment groups which will receive differing dosages of pneumococcus. The dose of organisms administered will be based on the preliminary study and will consist of the approximate LD50-75 dose and doses that are 10-fold higher and 10-fold lower than the approximate dose.

Dose-Response Studies of Anti-Pneumococcal Antibodies to Pneumococcal Polysaccharide In Splenectomized Rats.

One week after splenectomy, 15 rats will be divided into 5 groups with 3 animals per group and each group will receive 0.5, 1, 2, 4, or 6 ug 23-type polyvalent vaccine subcutaneously. Prior to immunization, each animal will be bled from the tail vein (~ 0.5 ml blood) and then bled on days 5, 7, 10, 15, and 21 post-immunization. Each serum sample will then be tested by ELISA for antibody titer to pneumococcal polysaccharide. Fifty (50) ul of diluted polyvalent mouse anti-pneumococcal polysaccharide antiserum will be added to each well of 96-well microtiter plates and incubated at 4°C for 18 hours. Each plate will then be washed, and 50 ul of the 23-type polyvalent polysaccharide diluted in 0.05M sodium

allowed to react at 37°C for 3 h. The plates will be washed and p-nitrophenyl phosphate substrate added. After incubation at 4°C for 18 h, 3.0 M NaOH will be added to each well to stop the reaction. Absorbance of colored substrate will be measured at 405 nm in a Biomek Automated Workstation (Beckman Instruments, Inc.). Results will be expressed as the end-point titration, defined as the highest dilution of serum producing an optical density in the test wells that was twice that of the same dilution in the control wells (pre-immune serum controls). This study is intended to establish optimal dose of polysaccharide to be used in terms of concentration and day of highest antibody response and to determine the isotype (IgM and/or IgG) of the antibody response.

Experiment 2: The purpose of the second part of the experiment will be to determine the effect of timing on the efficacy of pneumococcal vaccine. The study groups will consist of 24 rats each. Group 1 will undergo splenectomy and will receive sham subcutaneous injections at the same times as the vaccinated groups. Group 2 will undergo splenectomy and the predetermined dose of polyvalent pneumococcal vaccine will be administered one day following completion of the procedure. Group 3 will undergo splenectomy and vaccine will be administered one week after splenectomy. Group four will undergo splenectomy and vaccine will be administered six weeks postoperatively.
All groups will then be challenged with the predetermined dose of *S. pneumo.* 10 days after vaccination. Group 1 will be divided into three equal groups and will receive *S. pneumo.* at the same times as the vaccinated groups. One and 3 hours after infection, blood cultures will be drawn and analyzed in quantitative fashion to document clearance of the bacteria from the blood. In addition, blood will be drawn for ELISA determination of IgG levels 10 and 20 days after vaccination in all groups. Twenty days following vaccination, all surviving animals will be euthanized and lung and liver tissue cultured for measurement of bacterial counts per gram of tissue.

3. Animal Model for Passage of *S. pneumoniae*:
As a requirement to maintain organism virulence, an estimated 20 rats will be required for continuous passage of the pneumococcus organism in both experiments. The dose response curve will be performed on a subset of these rats.

Progress: This project was completed and the data is being analyzed. It appears that timing of pneumococcal vaccination after splenectomy does not affect survival with pneumococcal inoculation. However, IgG response is greater at 6 weeks.

DEPARTMENT OF SURGERY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ Martin A. Schrieber

PROTOCOL TITLE: A Randomized, Double-Blind, Multicenter Trial Assessing the Efficacy of Intravenous Cp-116,517 Followed by Oral Cp-99,219 Compared to Intravenous Imipenem/Cilastin Followed by Oral Amoxicillin/Clavulanic Acid for the Treatment of Complicated Intra-Abdominal Infections

PROTOCOL #95/59 STATUS: Completed

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): S Hetz

Keywords: Intra-abdominal Infections, Cp-116, 517, Oral Cp-99,219

Study Objective: To evaluate the safety and efficacy of intravenous CP-116,517 followed by oral CP-99,219 in the treatment of complicated intra-abdominal sepsis. This regimen will be compared to intravenous imipenem/cilastin followed by oral amoxicillin/clavulanic acid in a parallel group of patients. WBAMC'S role in this study will include patient recruitment, patient treatment, data collection and submission of data to PFIZER and the National Medicall Research Corporation.

Technical Approach: This is a prospective, randomized double-blind study comparing intravenous CP-116,517 and oral CP-99,219 to intravenous imipenem/cilastin followed by oral amoxicillin/clavulanic acid in patients with evidence of a systemic inflammatory response and proven intra-abdominal infection. The maximum length of total treatment will be 14 days. The efficacy of the two regimens will be evaluated based on clinical response and bacteriological response. All patients will be monitored for adverse effects of the two regimens.

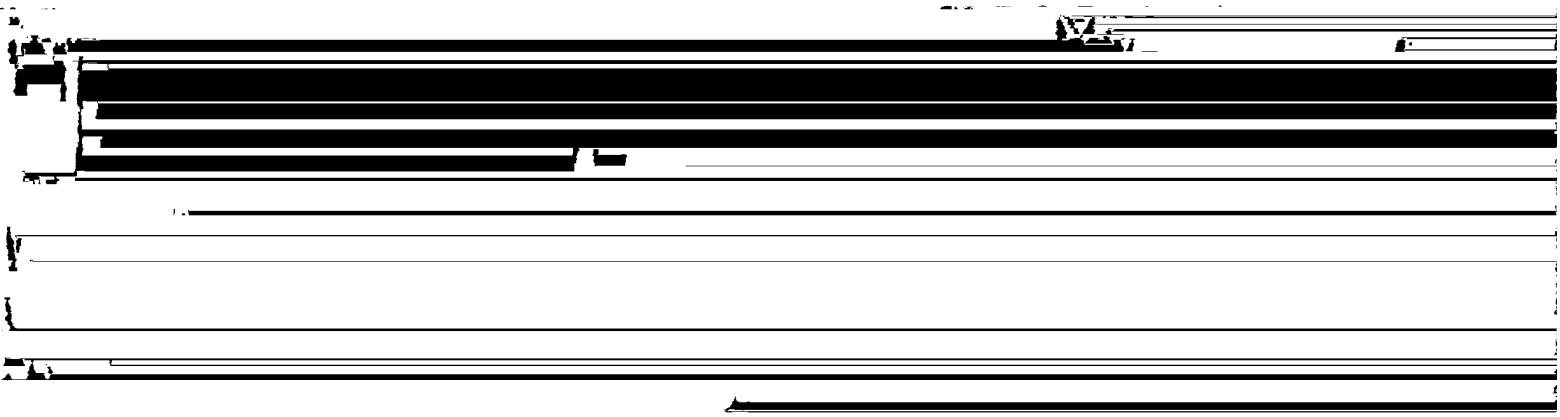
Progress: This study has been completed as of April 96. Total number of subjects entered is 2 and 1 who withdrew due to severe dizziness and nausea.

DEPARTMENT OF SURGERY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): COL Thomas J. Scully

PROTOCOL TITLE: Vascular Changes Associated with Stress Reaction of Bone in the Rat



FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): Ongoing

Key Words: Stress Reaction, Bone

Study Objective: To determine the sequence and character of vascular changes which occur in living bone after it has been subjected to repeated physical stress.

Technical Approach: We will study the character and chronological sequence of vascular changes which occur in rat legs subjected to mechanical stress in the absence of confounding electrical shocks.

a. Thirty anesthetized rats will have their left leg cyclicly mechanically stressed using the techniques of Scully et.al. The tibias will be cyclicly strained to 0.5 mm by repeated application of a 3 point bending load. 10,000 cycles of strain will be applied to the left tibia of each rat at a rate of 10 Hz. The animals will then be recovered from anesthesia and maintained in standard laboratory cages with unrestricted activity, on a standard laboratory diet. Groups of 2 animals will be selected at random on days 0, 1, 2, 3, 4, 5, 6, 7, 10, 12, 15, 18, 24 and 30 days after the initial strain loading.

b. On the date selected the animals will be anesthetized with Nembutal at a dose of 25mg/kg intravenously. The rats will then be heparinized and injected with Xylocaine to prevent vascular thrombosis and to ensure maximum vasodilation. The animals will then be given a lethal dose of Nembutal. After euthanasia the abdomens will be opened through a midline abdominal incision. The aorta and inferior vena cava will be transected and cannulated. Using techniques prescribed in the Microfil product literature the aorta and both lower extremities will be perfused with Microfil at a pressure of 150 mm of mercury. Perfusion will continue until the flow of the Microfil is returned via the inferior vena cava. At that point the animals will be refrigerated to allow overnight curing of the Microfil. As each animal has had only one leg stressed, the contralateral leg will serve as a control. Radiographs will be taken of both lower extremities to delineate the microvascular structure. Microfil is a radio-opaque material. After the radiographs are obtained, tissue clearing will be performed by the following technique: on the first day both tibias will be immersed in a 25% ethanol solution. On the second day 50% ethanol, on the third 75% ethanol, on the fourth day 95% ethanol and on the fifth day a new solution of absolute alcohol. On the sixth day the specimen will be immersed for 24 hours in methylsalicylate. If the tissue is not clear it will be returned to a 95 % ethanol solution and the fine cleaning procedure steps will be repeated. Photographs will then be taken of the vascular tree which will have been filled with colored Microfil. The tibias will then be imbedded and sectioned for standard histologic sectioning.

DEPARTMENT OF SURGERY

DETAIL SUMMARY SHEET SEPTEMBER 1996

PRINCIPAL INVESTIGATOR(S): MAJ William R. Stevens

PROTOCOL TITLE: The Use of Demineralized Bone Matrix and Titanium Cage in Interbody Fusion of the Spine using the Goat (*Capra hircus*) Model.Include animal species in title. Example: Evaluation of Suture Patterns with Silk in the Laboratory Mouse (Mus musculus)

PROTOCOL #95/55A STATUS: Ongoing

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): L Hoban-Stevens, R Copeland, G Gil, J Cartwright

Keywords: Spinal Fusion, Animal Models

Study Objective: To determine the effectiveness of a new demineralized bone matrix (DBM) and titanium mesh cage (TMC) construct in achieving anterior interbody fusion of the spine in a goat model.

Technical Approach: For some injuries of the spinal column, a common surgical procedure is to attempt to fuse the bones of the affected area to provide a stable section of the spinal column to relieve the patient's pain, other symptoms, and worsening of the condition. In the past, surgeons have used many techniques to produce this fusion. Of the current techniques, packing of the affected section of the spinal column with bone taken from the hip or enclosing the area in a special rigid metal cage is popular. Both of these techniques have a number of problems. One of the biggest problems is not achieving the fusion of the area.

This study will combine the use of a special rigid metal cage with a new form of specially processed bone material on a created spinal column defect that requires fusion. The bone material should offer many important advantages over bone donated from the patient's hip. The most probable advantage should be greatly increased healing of the defect and production of an excellent fusion. Twenty goats will be used to test the new bone material in the both the neck and chest areas of the spinal column. If fast fusion results occur as expected, this study would be an important step in getting the new bone material into human trials.

Progress: Animal implantations completed as of 1/31/97. Harvest of specimens 5/97. This study is currently being continued until 31 Jun 97.
Amendments 1& 2, dated 16 Jan 95 were submitted by Dr. Stevens.
Changes in protocol include:
Amendment 1. The cervical portion of the study is to be deleted for the 23 animals enrolled in this study. The investigators may wish to undertake this portion of the study separately, at a later date. This change will avoid potentially higher morbidity and mortality rate in the test population.
Amendment 2. The investigators wish to add a third level in the lumbar spine as a negative control. At this level, a third titanium cage will be filled with Gelfoam. This material has hemostatic properties, and is commonly used to control bony bleeding in spinal and other orthopedic procedures. Gelfoam has no activity as an osteo-inductive or osteo-conductive material, produces no inflammatory response, and is ultimately absorbed by the body. Gelfoam also has no known inhibitory effects on bone formation. It is therefore anticipated that fusion would be inhibited at this level by the neutral spacer affect of the Gelfoam. The absence or delay of fusion at this level will serve to validate the study by proving that spontaneous fusion does not occur in the lumbar spine of goats.

DCI

WBAMC, El Paso, TX